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Outcomes of limited stage primary bone diffuse large B-cell lymphoma in the rituximab era: a multicenter, retrospective study

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**Key words:** primary bone, lymphoma, real-world, radiation, rituximab
Abstract
Primary bone diffuse large B cell lymphoma (DLBCL) is a rare variant of extranodal non-Hodgkin lymphoma (NHL) historically treated with induction chemotherapy followed by consolidative radiation therapy (RT). It remains unknown whether RT confers additional benefit following rituximab-based chemoimmunotherapy (CIT) induction in patients with limited-stage disease. We conducted a multicenter retrospective analysis of patients treated between 2005 and 2019 using rituximab-based CIT regimens with or without consolidative RT to discern whether consolidative RT adds benefit in patients with stage I-II disease that could be encompassed in one radiation field. A total of 112 patients were included: 78 received CIT and radiation (RT group), and 34 received CIT alone (no RT group). The OS at 10 years was 77.9% in the RT group and 89.0% in the no RT group (p = 0.42). The RFS at 10 years was 73.5% in the RT group and 80.3% in the no RT group (p = 0.88). Neither improved OS nor RFS was associated with the addition of consolidative RT. Subgroup analysis of patients only achieving a partial response after CIT suggests that these patients may benefit from consolidative RT.

Introduction
Primary bone diffuse large B cell lymphoma (DLBCL) is a variant of extranodal non-Hodgkin lymphoma (NHL) that is relatively rare, accounting for 3-15% of extranodal NHL and less than 1% of all NHL.1,2 It has been previously defined as single- or multifocal lymphomatous lesion(s) in the bone, without lymph node or visceral disease. This can make classification of the disease challenging when there is adjacent soft tissue involvement or regional lymph node disease.1 Current staging systems utilize the Lugano Modification of the Ann Arbor Staging System, with the classification into four stages as follows: stage I-E constitutes a single bony lesion without nodal involvement; stage II-E constitutes a single bony lesion plus at least one lymph node or group of adjacent lymph nodes; stage IV-E constitutes multifocal disease in a single bone or lesions in multiple bones without nodal involvement; stage IV is characterized by disseminated lymphoma with at least one bone lesion.3

Patients with primary bone DLBCL often present with pain and swelling of the affected area of the skeleton, with B symptoms being less prevalent.1 Patients may present with pathologic fracture, and the femur is the most common site of disease.2 The median age of disease onset is during the 5th decade of life, and it is slightly more predominant in men compared to women.2,4

From the time lymphoma of the bone was first described in 1939 until the mid-20th century, the cornerstone of treatment was radiation therapy.5 Chemotherapy regimens were then introduced in the 1970s and used in combination with radiation, often referred to as combined modality therapy (CMT). Traditional regimens were typically CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), or CHOP-like. For limited stage DLBCL in general, a standard of care regimen was ultimately established with the Southwest Oncology Group (SWOG) study S8736, which showed that three cycles of CHOP followed by RT had superior PFS and OS rates compared to eight cycles of CHOP alone.6 With the advent of rituximab in the late 1990s and subsequent trials7-9 illustrating its efficacy in improving overall survival (OS) and disease-free survival (DFS) when added to traditional chemotherapy regimens for systemic DLBCL, it gradually became standard of care for the treatment of all DLBCL. Notably, SWOG S0014 showed that rituximab plus CHOP for three cycles and involved field RT in patients with limited-stage DLBCL was a safe regimen, with a 2-year PFS rate of 84%.10

Specifically for primary bone DLBCL, earlier studies showed CMT to be superior to radiation therapy, with improvement in OS and relapse-free survival (RFS).11-13 Other non-randomized/retrospective studies suggested that the inclusion of radiation therapy may improve outcomes.14-16 However, this literature has significant limitations in that many of the studies were completed prior to the rituximab era, some included advanced stage patients, and most included multiple NHL subtypes owing to the rarity of primary bone DLBCL. The inclusion of patients with advanced stage disease complicates interpretation, since patients with advanced disease often have non-synchronous bony lesions and bulky disease for which RT could provide a palliative rather than survival benefit, and often times RT is not consistently directed to the primary lesion.15
In the rituximab era, for limited stage DLBCL in general, some studies have aimed to eliminate RT in select patients. For example, SWOG S1001 omitted RT in interim PET-negative patients and demonstrated similar outcomes to those with interim PET-positive disease receiving RT. A similar PET-directed retrospective study was conducted in British Columbia and showed congruent results. The FLYER study is another radiation-free regimen that examined whether less chemotherapy could be safely administered to aggressive B-cell NHL patients 18-60 years of age who had non-bulky (<7.5 cm), limited stage disease (I-II), and found that 4 cycles of R-CHOP was non-inferior to 6 cycles and was less toxic. However, extrapolating these PET-directed studies of limited stage DLBCL to primary bone DLBCL presents a unique challenge in several regards. First, PET interpretation in the setting bone healing and sclerosis post-treatment can be difficult. Second, only a small portion of the patients included in these studies had primary bone DLBCL. Therefore, we sought to investigate the utility of consolidative RT in the rituximab era in patients with primary bone DLBCL.

We performed a multicenter retrospective study to analyze outcomes of patients with limited-stage (stage I-E and stage II) primary bone DLBCL, comparing those who received CIT plus RT to those who received CIT alone in order to determine whether the addition of radiation confers benefit. We also evaluated the subgroup of patients achieving a partial response (PR) after CIT, to determine if that group may benefit from consolidative RT. Our study includes patients from multiple academic medical centers in the United States, focusing only on those who were treated with rituximab-based CIT.

**Methods**

We conducted a multicenter retrospective analysis of outcomes in a modern cohort of patients who underwent treatment for primary bone DLBCL using chemotherapy regimens in the rituximab era either with or without consolidative RT. We obtained initial Institutional Review Board (IRB) approval at the main site, then obtained subsequent approval at partnering sites, some of which required data use agreements (DUAs) per individual institutional policy. Data were collected from 13 academic medical centers in the U.S., with patients treated between 2005 and 2019. Each center generated a list of participants using the inclusion and exclusion criteria outlined below. Data collection occurred independently at each center using their available electronic medical record. The coordinating center provided data sheet for data entry as well as a similar data sheet with identifying information removed to be used for correspondence with the coordinating center. All de-identified data was aggregated and analyzed at the coordinating center.

Eligible patients were 18 years of age or older and had stage I-E or stage II-E primary bone DLBCL. Stage II patients were only included if they had locoregional lymph node involvement that could be encompassed in a single radiation field. Patients had histologically confirmed primary DLBCL and high-grade B-cell lymphoma per the individual institution’s records. Independent or centralized pathologic verification of diagnosis was not performed since all specimens had already undergone review by an expert hematopathologist. Imaging response was reviewed at each institution; there was no centralized imaging review. Response criteria were according to the Lugano lymphoma response criteria. Patients with stage IV disease were excluded, as were those with post-transplant lymphoproliferative disorder.

Chi-square analysis was used to compare categorical variables. The Wilcoxon rank-sum test was used for continuous and ordinal measures. Survival curves were estimated using the Kaplan-Meier method and compared the groups via the log-rank test. Multi-variable analysis (MVA) using Cox regression was used for OS and RFS using RT and no RT, and dose of RT <36 Gy vs ≥36 Gy.

Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). The radiotherapy-based groups were defined on observed treatment as no intent-to-treat information was available. However, any immortal time bias was expected to be low as there are no observed deaths during the treatment period. Patients were followed for survival from the time of diagnosis to death or last follow up by any provider. Follow up was administratively censored at 10 years due to the low number of patients under follow up at that time.
Results

Patient characteristics

The demographic information and baseline characteristics of the patients included in the analysis is listed in Table 1. A total of 112 patients were included and divided into those who received CIT and radiation (RT group, 78 patients) and those who received CIT only (no RT group, 34 patients). Characteristics were balanced among the groups, such as age, gender, B symptoms, elevated LDH, National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) score, and stage I versus II disease. Clinical features at the time of diagnosis such as fracture, bone pain, and cord compression occurred at a similar rate between the two groups. There was a significant difference noted between the groups with regard to number of chemotherapy cycles, with the RT group receiving a mean number of 4.5 cycles and the no RT group receiving a mean number of 5.6 cycles (p<0.001). Most patients (92%) had low or low-intermediate IPI risk disease.

Clinical outcomes

There was no difference in OS between the RT and no RT groups (Figure 1A). The 10-year overall survival rate for the RT group was 77.9% versus 89.0% for the no RT group (p = 0.42). Similarly, there was no difference in RFS between these groups, with a 10–year RFS of 73.5% for the RT group versus 80.3% for the no RT group (p = 0.88, Figure 1B). Lymphoma was only a cause of death in a minority of cases: 2 of the 9 cases in the RT group, and 0 of the 2 cases in the no RT group. Median follow up was 66.3 months in all patients, with 70.4 months in the RT group and 65.0 months in the no RT group (Table 1).

There were 8 patients who achieved a PR with CIT. Of these patients, 6 were then treated with RT, 5 of whom then converted to a CR. The median duration of response for these patients was 49 months (range 12 – 71.5 months).

Analysis of radiation dose received

The RT group was further stratified based on dose of radiation received. There was no difference in OS between those who received ≥ 36 Gy compared to those who received < 36 Gy (Figure 1C). The 10-year OS for the ≥ 36 Gy group was 75.1%, compared to 90.9% for the < 36 Gy group (p = 0.77). Similarly, there was no difference in RFS between these groups, with a 10-year RFS rate of 70.9% for the ≥ 36 Gy group and 85.6% for the < 36 Gy group (p = 0.84, Figure 1D).

Discussion

In this study, we did not find an OS or RFS benefit associated with the addition of radiation therapy to CIT in patients with stage I and localized stage II primary bone DLBCL. In addition, among the patients who received RT, there was no improvement in outcomes for those who received higher doses of RT (≥ 36 Gy). Among patients achieving a PR to CIT, 5 out of 6 patients who then went on to receive consolidative RT achieved a complete response, suggesting that RT may be particularly useful in this patient subgroup. The 10-year OS rate in all groups was greater than 70%, illustrating that patients with this disease overall have favorable outcomes with modern therapy.

Combined modality therapy for primary bone DLBCL has been examined in several previous studies. For example, the IELSG-14 study conducted by Bruno-Ventre et al. in 2014 was a retrospective study of 161 patients with limited stage primary bone DLBCL. The authors found that anthracycline-based chemotherapy conferred a more favorable prognosis compared to those treated with radiotherapy alone, and that the addition of radiation in doses larger than 36 Gy was not beneficial.20 This study also found that chemotherapy followed by radiotherapy resulted in better outcomes compared to radiotherapy followed by chemotherapy. Of note, most patients this study were treated in the pre-rituximab era. A multicenter retrospective study conducted by the Rare Cancer Network (RCN) in 2011 which examined
patients with stage I and II primary bone lymphoma (78% DLBCL) revealed that combined modality therapy, as well as doses of radiation greater than 40 Gy, resulted in improved prognosis by univariate analyses. However, only 28% of patients received rituximab-based CIT, with 60% receiving chemotherapy, and 12% receiving radiation alone. A prospective Australian study of primary bone NHL (97% DLBCL) was conducted by Christie et al. in 2011, in which patients received three cycles of CHOP followed by 45 Gy of radiation, regardless of response to chemotherapy, illustrated 5-year OS of 90% and a local control rate of 72%. It should be noted that this study closed early as rituximab became more readily available, and over the entire time of study accrual, only 19% of patients received rituximab in addition to their chemotherapy. Overall, though these studies utilized varying radiation doses, all generally suggest a benefit of CMT in patients largely treated without rituximab.

Current guidelines for radiation treatment of limited stage DLBCL recommend doses of 30-36 Gy if patients achieve a complete remission (CR) after CIT, and higher doses of 40-50 Gy for those who achieve a partial remission (PR). Multiple studies have been conducted to further examine the benefits of increased doses of RT: Lee et al. conducted a retrospective study that included patients with stage I/II - IV DLBCL and osseous involvement, with the aim to discern whether higher doses of RT are beneficial, and found that 20-30 Gy is sufficient for those who achieve a CR and higher doses should be reserved for those who attain a PR. Tao et al. found no difference in OS or PFS in patients who received 36 Gy compared to those who received 30 – 35 Gy. Both of these studies included patients prior to the rituximab era and with stage I – IV disease, thus the findings are not completely applicable to patients in our study. It is important to note that consolidative RT does not come without risk, including risk of gastrointestinal/mucosal toxicity, secondary malignancies, and dental-related toxicities for lesions located in the head and neck region. At some of the centers in our study, it was common practice to only employ RT if patients had a PR after CIT, thus exemplifying variability in practice across institutions. Based on this mode of practice, it is possible that patients who do not attain a CR (and therefore perhaps have more intrinsically aggressive disease), could obtain some benefit from RT. Indeed, our data revealed that among the 6 patients who only achieved a PR with CIT and then went on to receive RT, 83% achieved a CR. This suggests that consolidative RT may confer benefit in patients who only achieve a PR with CIT induction.

This study is subject to limitations, in part due to its retrospective design. Additionally, we were not able to ascertain the reason why patients received or did not receive RT, or why some patients received higher doses of RT. This could have introduced a provider bias regarding which patients were selected to receive RT. In addition, the study spans a relatively long timeframe; various aspects of care such as radiation therapy techniques and supportive care have evolved during that time, potentially affecting outcomes. To conclusively answer the question of whether consolidative RT confers benefit in some patients (or perhaps just in patients achieving PR after CIT), a prospective randomized trial would need to be conducted; however, this would be challenging given the low incidence of primary bone DLBCL.

In conclusion, patients with limited-stage primary bone DLBCL treated in the rituximab era have excellent outcomes overall. The addition of radiation does not appear to improve these outcomes in general, although we cannot rule out that a subset of patients (e.g., those achieving PR with CIT) may benefit from consolidative radiation.
References


## Table

**Table 1:** Demographics, treatment, and follow-up results of the total 112 patients, divided into CIT followed by RT (RT group) vs CIT alone (no RT group). NCCN-IPI = National Comprehensive Cancer Network International Prognostic Index, CIT = chemoimmunotherapy, W = Wilcoxon rank sum test, C = Chi-square test, T = T-test, + = Exact test, SD = standard deviation. Values in parentheses are %, unless otherwise noted.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total, N = 112 (%)</th>
<th>RT, N = 78 (%)</th>
<th>No RT, N = 34 (%)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Females</td>
<td>57 (50.9)</td>
<td>40 (51.3%)</td>
<td>17 (50.0)</td>
<td>1.000*</td>
</tr>
<tr>
<td>Males</td>
<td>55 (49.1)</td>
<td>38 (48.7%)</td>
<td>17 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>58.0 (18.0-86.0)</td>
<td>55.0 (20.0-86.0)</td>
<td>58.5 (18.0-86.0)</td>
<td>0.420*</td>
</tr>
<tr>
<td>NCCN-IPI, Low Risk (0-1)</td>
<td>74 (71.8)</td>
<td>49 (70)</td>
<td>25 (71.5)</td>
<td></td>
</tr>
<tr>
<td>NCCN-IPI, Low-Intermediate Risk (2-3)</td>
<td>28 (27.2)</td>
<td>21 (30)</td>
<td>7 (21.2)</td>
<td></td>
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<tr>
<td>NCCN-IPI, High-Intermediate Risk (4-5)</td>
<td>1 (1.0)</td>
<td>0 (0)</td>
<td>1 (3.0)</td>
<td>0.801*</td>
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<tr>
<td>Unknown NCCN-IPI score</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>B symptoms</td>
<td>7 (6.3)</td>
<td>3 (3.8)</td>
<td>4 (12.1)</td>
<td>0.193**</td>
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<tr>
<td>Elevated LDH</td>
<td>30 (30.6)</td>
<td>25 (36.8)</td>
<td>5 (16.7)</td>
<td>0.047c</td>
</tr>
<tr>
<td>Fracture at presentation</td>
<td>18 (16.1)</td>
<td>15 (19.2)</td>
<td>3 (8.8)</td>
<td>0.168c</td>
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<td>Bone Pain at presentation</td>
<td>100 (90.9)</td>
<td>70 (92.1)</td>
<td>30 (88.2)</td>
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<tr>
<td>Cord Compression at presentation</td>
<td>7 (6.3)</td>
<td>6 (7.7)</td>
<td>1 (2.9)</td>
<td>0.437**</td>
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<tr>
<td>Pathology with DLBCL</td>
<td>110 (98.2)</td>
<td>76 (97.4)</td>
<td>34 (100.0)</td>
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<td>Pathology with Aggressive B cell lymphoma, not otherwise specified (NOS)</td>
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<td>2 (2.6)</td>
<td>0 (0.0)</td>
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<td>Stage I</td>
<td>89 (79.5)</td>
<td>64 (82.1)</td>
<td>25 (73.5)</td>
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<tr>
<td>Stage II</td>
<td>23 (20.5)</td>
<td>14 (17.9)</td>
<td>9 (26.5)</td>
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<td>RT dose ≥ 36 Gy</td>
<td>57 (52.8)</td>
<td>57 (77.0)</td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>RT dose &lt; 36 Gy</td>
<td>17 (15.7)</td>
<td>17 (23.0)</td>
<td>(-)</td>
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</tr>
<tr>
<td>Mean number of chemotherapy cycles, (+/- SD)</td>
<td>4.8 (+/- 1.4)</td>
<td>4.5 (+/- 1.4)</td>
<td>5.6 (+/- 1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median follow up (months)</td>
<td>66.3 (6.9 - 120.0)</td>
<td>70.4 (8.3 - 120.0)</td>
<td>65.0 (6.9 - 120.0)</td>
<td>0.745*</td>
</tr>
</tbody>
</table>

## Figure Legend

**Figure 1:** Kaplan-Meier curves of primary outcomes of relapse-free survival and overall survival. A: Relapse-free survival of RT and no RT groups. B: Overall survival of RT and no RT groups. C: Relapse-free survival of patients who received ≥ 36 Gy RT and those who received < 36 Gy. D: Overall survival of patients who received ≥ 36 Gy RT and those who received < 36 Gy. LFU = last follow-up.