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

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Abstract

Primary bone diffuse large B-cell lymphoma is a rare variant of extranodal non-Hodgkin lymphoma 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 overall survival at 10 years was 77.9% in the RT group and 89.0% in the no RT group (*P*=0.42). The relapse-free survival at 10 years was 73.5% in the RT group and 80.3% in the no RT group (*P*=0.88). Neither improved overall survival nor relapse-free survival 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 three 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 adjacent or regional lymph node;multi-focal bony disease (with or without nodal disease) is classified as stage IV.[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 pathological fractures with the femur being the most common site of disease.[2] The median age of disease onset is during the fifth decade of life, and this form of lymphoma is slightly more common in men than in 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 produced superior progression-free survival and overall survival (OS) rates compared to those achieved

with eight cycles of CHOP alone.[6] With the advent of rituximab in the late 1990s and subsequent trials[7-9] illustrating its efficacy in improving OS and disease-free survival 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 progression-free survival rate of 84%.[10]

Specifically for primary bone DLBCL, earlier studies showed that CMT was superior to RT, with improvements in OS and relapse-free survival (RFS).[11-13] Other non-randomized/retrospective studies suggested that the inclusion of RT 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 patients with advanced stage disease, and most included multiple NHL subtypes because of the rarity of primary bone DLBCL. The inclusion of patients with advanced stage disease complicates interpretation of the findings, 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 selected patients. For example, SWOG S1001 omitted RT in patients who were negative for disease according to an interim positron emission tomography (PET) assessment and demonstrated that these patients had similar outcomes to those with interim PET-positive disease receiving RT.[17] A similar PET-directed retrospective study was conducted in British Columbia and showed congruent results.[18] The FLYER study is another radiation-free regimen that examined whether less chemotherapy could be safely administered to patients with aggressive B-cell NHL 18-60 years of age who had non-bulky (<7.5 cm), limited stage disease (stage I-II), and found that four cycles of CHOP plus rituximab (R-CHOP) was not inferior to six cycles and was less toxic.[19] However, extrapolating the results of these PET-directed studies of limited stage DLBCL to primary bone DLBCL presents a unique challenge in several regards. First, interpreting PET findings in the setting of bone healing and sclerosis after treatment can be difficult. Second, only a small proportion 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 (RT group) to those who received CIT alone (no RT group) 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 included patients from multiple academic medical centers in the USA, 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 approval at the main site, then obtained subsequent approval at partnering sites, some of which required data use agreements per individual institutional policy. Data were collected from patients treated between 2005 and 2019 in 13 academic medical centers in the USA. Each center generated a list of participants using the inclusion and exclusion criteria outlined below. Data were collected independently at each center using the center's already existing electronic medical records. The coordinating center provided a 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 were 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 loco-regional lymph node involvement that could be encompassed in a single radiation field. Patients had histologically confirmed primary DLBCL and high-grade B-cell lymphoma according to the individual institutions' records. Independent or centralized pathological verification of the 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 was classified 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 the groups were compared via the log-rank test. Multivariable analysis by Cox regression was used for OS and RFS comparing the RT group *versus* the no RT group and doses of RT <36 Gy *versus* ≥36 Gy.

Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). The RT-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 no deaths were observed 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 after that time.

Results

Patients' characteristics

The demographic information and baseline characteristics of the patients included in the analysis are 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). The groups were balanced for characteristics such as age, gender, B symptoms, elevated lactate dehydrogenase, 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 similar rates in the two groups. There was, however, a statistically 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 OS 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: two of the nine cases in the RT group, and neither of the two cases in the no RT group. The median follow up was 66.3 months in all patients, being 70.4 months in the RT group and 65.0 months in the no RT group (Table 1).

Eight patients achieved a PR with CIT. Of these patients, six were subsequently treated with RT, five of whom then converted to a complete response (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

Table 1. Demographics, treatment, and follow-up results of the total 112 patients and these patients divided according to whether they received chemoimmunotherapy followed by radiotherapy (RT group) or chemoimmunotherapy alone (no RT group).

| Characteristics	All patients N=112	RT group N=78	No RT group N=34	*P*
Sex, N (%) Females Males	 57 (50.9) 55 (49.1)	 40 (51.3) 38 (48.7)	 17 (50.0) 17 (50.0)	1.000[C+]
Age at diagnosis in years, median (range)	58.0 (18.0-86.0)	55.0 (20.0-86.0)	58.5 (18.0-86.0)	0.420[W]
NCCN-IPI risk group, N (%) Low-risk, 0-1 Low-intermediate risk, 2-3 High-intermediate risk, 4-5 Unknown	 74 (71.8) 28 (27.2) 1 (1.0) 9	 49 (70) 21 (30) 0 (0) 8	 25 (71.5) 7 (21.2) 1 (3.0) 1	0.801[W]
B symptoms, N (%)	7 (6.3)	3 (3.8)	4 (12.1)	0.193[C+]
Elevated LDH, N (%)	30 (30.6)	25 (36.8)	5 (16.7)	0.047[C]
Fracture at presentation, N (%)	18 (16.1)	15 (19.2)	3 (8.8)	0.168[C]
Bone pain at presentation, N (%)	100 (90.9)	70 (92.1)	30 (88.2)	0.721[C+]
Cord compression at presentation, N (%)	7 (6.3)	6 (7.7)	1 (2.9)	0.437[C+]
Pathology with DLBCL, N (%)	110 (98.2)	76 (97.4)	34 (100.0)	-
Pathology with aggressive B-cell lymphoma, not otherwise specified, N (%)	2 (1.8)	2 (2.6)	0 (0.0)	0.010[C+]
Disease stage, N (%) I II	 89 (79.5) 23 (20.5)	 64 (82.1) 14 (17.9)	 25 (73.5) 9 (26.5)	0.305[C]
Radiotherapy dose group, N (%) ≥36 Gy <36 Gy	 57 (52.8) 17 (15.7)	 57 (77.0) 17 (23.0)	 - -	NA
N of chemotherapy cycles, mean (±SD)	4.8 (±1.4)	4.5 (±1.4)	5.6 (±1.1)	<0.001
Follow up in months, median (range)	66.3 (6.9-120.0)	70.4 (8.3-120.0)	65.0 (6.9-120.0)	0.745[W]

NCCN-IPI: National Comprehensive Cancer Network International Prognostic Index; LDH: lactate dehydrogenase; DLBCL: diffuse large B-cell lymphoma; W: Wilcoxon rank sum test, C: χ² test; +: exact test; NA: not applicable; SD: standard deviation.

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 RT 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, five out of six pa-

tients who then went on to receive consolidative RT achieved a CR, suggesting that RT may be particularly useful in this subgroup of patients. The 10-year OS rate in all groups was greater than 70%, illustrating that, overall, patients with this disease have favorable outcomes with modern therapy.

Several previous studies have examined CMT for primary bone DLBCL. For example, the IELSG-14 study conducted by Bruno-Ventre *et al.* in 2014 was a retrospective analysis of 161 patients with limited stage primary bone DLBCL. The authors found that anthracycline-based chemotherapy conferred a more favorable prognosis compared to that of treatment with RT alone, and that the addition of radiation in doses greater than 36 Gy was not beneficial.[20] This study also found that chemotherapy followed by RT resulted in better outcomes compared to RT followed by chemotherapy. Of note, most patients in that study were treated in the pre-rituximab era.
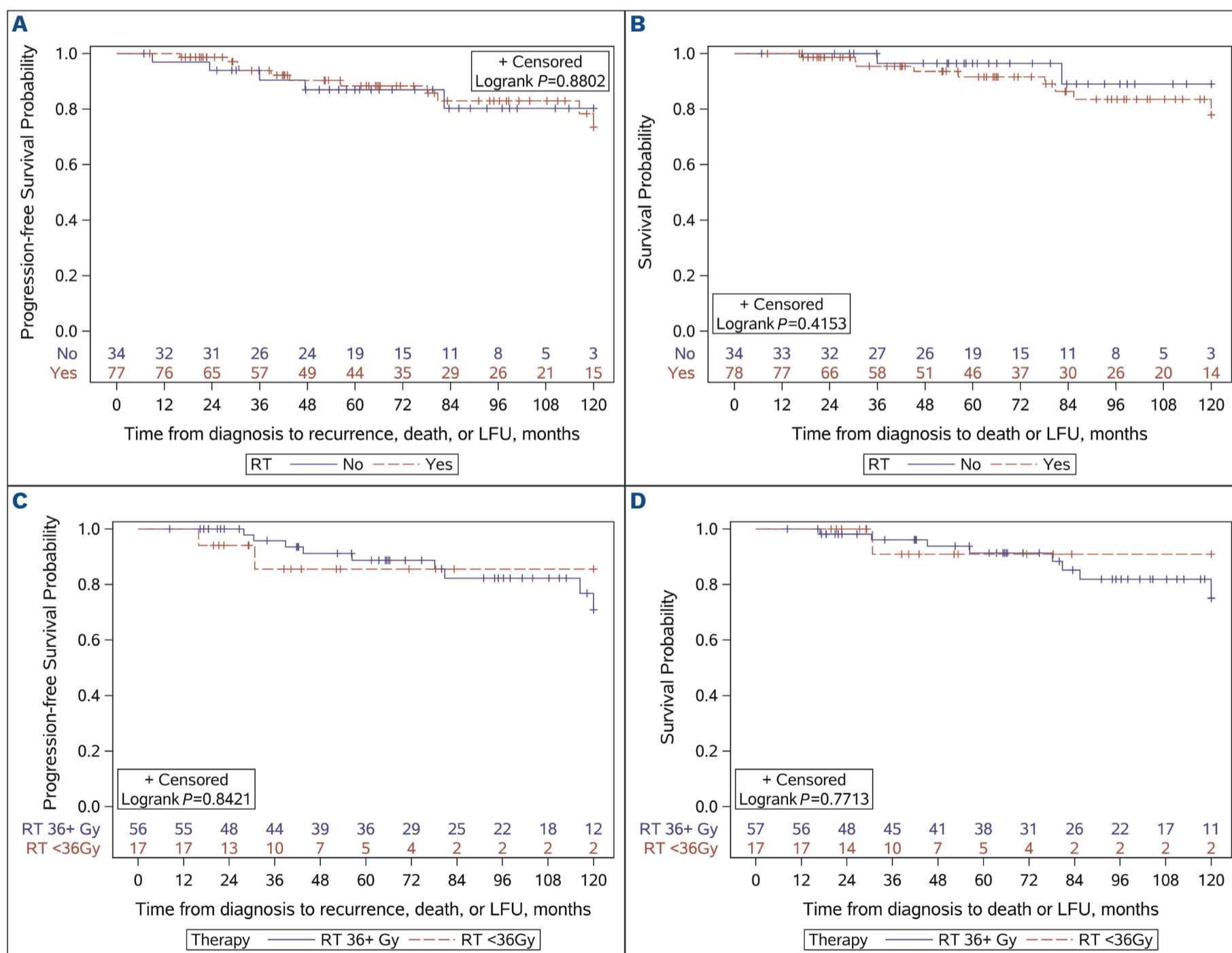
Figure 1. Kaplan-Meier curves of primary outcomes of relapse-free survival and overall survival. (A) Relapse-free survival of patients divided according to whether they did or did not receive radiation therapy (RT). (B) Overall survival of patients divided according to whether they did or did not receive RT. (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.

A multicenter, retrospective study conducted by the Rare Cancer Network in 2011 which examined patients with stage I and II primary bone lymphoma (78% DLBCL) revealed that CMT, as well as doses of radiation greater than 40 Gy, resulted in improved prognosis by univariate analyses.[16] 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 their study, patients received three cycles of CHOP followed by 45 Gy of radiation, regardless of response to chemotherapy, and had a 5-year OS of 90% and a rate of local disease control of 72%.[21] 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, although these studies utilized varying radiation doses, all generally suggest a benefit of CMT in patients largely treated without rituximab. Current guidelines for RT of limited stage DLBCL recommend doses of 30-36 Gy if patients achieve a CR after CIT, and higher doses of 40-50 Gy for those who achieve a PR.[22] Multiple studies have been conducted to further examine the benefits of increased doses of RT. For example, Lee *et al.* conducted a retrospective study that included patients with stage I/II-IV DLBCL and osseous involvement, with the aim of determining whether higher doses of RT are beneficial, and found that 20-30 Gy are sufficient for those who achieve a CR and higher doses should be reserved for those who attain a PR.[23] Tao *et al.* found no difference in OS or progression-free survival in patients who received 36 Gy compared to those who received 30-35 Gy.[14] Both of these studies included patients prior to the rituximab era and with stage I-IV disease, thus the findings are not completely comparable to those of our study. It is important to note that consolidative RT does not come without risks, including those of gastrointestinal/mucosal toxicity, secondary malignancies, and dental-related toxicities for lesions located in the head and neck region.[15,23] At some of the centers in our study, it was common practice to administer 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, of the six 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 has some limitations, in part due to its retrospective design. For example, 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. Furthermore, the study spans a relatively long timeframe; various aspects of care such as RT techniques and supportive care have evolved during that period, 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.

Disclosures

Contributions

AR collected on-site data, collated the data from the sites, and wrote the paper. AS analyzed the results and made the figures. AK, DJI, MAL, NLB, PFC, TDR, PMB, SMC, NE, HM, BT, TSO, RK, JEC, GG, BMP, KMI, and CAP contributed data from individual sites and contributed to the manuscript. KM assisted in planning the study and collated data from the sites. MS and DMK contributed data from the main site and contributed to the manuscript. TSF designed the study, interpreted the results, and co-authored the paper.

Data-sharing statement

The data that support the findings of this study are available from the corresponding author, TSF, upon reasonable request.

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