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ORIGINAL REPORT

Impact of Rituximab and Radiotherapy on Outcome of Patients With Aggressive B-Cell Lymphoma and Skeletal Involvement

Gerhard Held, Samira Zeynalova, Niels Murawski, Marita Ziepert, Barbara Kempf, Andreas Viardot, Martin Dreyling, Michael Hallek, Mathias Witzens-Harig, Jochen Fleckenstein, Christian Rübe, Carsten Zwick, Bertram Glass, Norbert Schmitz, and Michael Pfreundschuh

Gerhard Held, Niels Murawski, Jochen Fleckenstein, Christian Rübe, and Michael Pfreundschuh, Saarland University Medical School; Bertram Glass and Norbert Schmitz, Asklepios-Klinik St. Georg, Hamburg; Samira Zeynalova and Marita Ziepert, Leipzig University, Leipzig; Barbara Kempf, Klinikum Landshut, Landshut; Andreas Viardot, Universitätsklinikum Ulm, Ulm; Martin Dreyling, Ludwig-Maximilian University, Munich; Michael Hallek, Cologne University, Cologne; and Mathias Witzens-Harig, Heidelberg University, Heidelberg, Germany.

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Both G.H. and S.Z. contributed equally to this work.

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Corresponding author: Michael Pfreundschuh, MD, Internal Medicine I, Saarland University Medical School, D-66421 Homburg (Saar), Germany; e-mail: michael.pfreundschuh@uks.eu.

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ABSTRACT

Purpose
To study clinical presentation, outcome, and the role of radiotherapy in patients with aggressive B-cell lymphoma and skeletal involvement treated with and without rituximab.

Patients and Methods
Outcome of patients with skeletal involvement was analyzed in a retrospective study of nine consecutive prospective trials of the German High-Grade Non-Hodgkin lymphoma Study Group.

Results
Of 3,840 patients, 292 (7.6%) had skeletal involvement. In the MabThera International Trial (MInT) for young good-prognosis patients and the Rituximab With CHOP Over 60 Years (RICOVER-60) study for elderly patients, the randomized addition of rituximab improved event-free survival (EFS; hazard ratio for MInT [HR_{MInT}] = 0.4, $P > 001$; hazard ratio for RICOVER-60 [$HR_{RICOVER-60}$] = 0.6, $P > .001$) and overall survival (OS; $HR_{MInT} = 0.4$, $P < .001$; $HR_{RICOVER-60} = 0.7$, $P = .002$) in patients without skeletal involvement, but failed to improve the outcome of patients with skeletal involvement (EFS: $HR_{MInT} = 1.4$, $P = .444$; $HR_{RICOVER-60} = 0.8$, $P = .449$; OS: $HR_{MInT} = 0.6$, $P = .449$; $HR_{RICOVER-60} = 1.0$, $P = .935$). Skeletal involvement was associated with a worse outcome after cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus rituximab ($HR_{EFS} = 1.5$, $P = .048$; $HR_{OS} = 1.1$; $P = .828$), but not after CHOP without rituximab ($HR_{EFS} = 0.8$, $P = .181$; $HR_{OS} = 0.7$, $P = .083$). In contrast to rituximab, additive radiotherapy to sites of skeletal involvement was associated with a decreased risk ($HR_{EFS} = 0.3$, $P = .001$; $HR_{OS} = 0.5$; $P = .111$).

Conclusion
Rituximab failed to improve the outcome of patients with diffuse large B-cell lymphoma with skeletal involvement, although our data suggest a beneficial effect of radiotherapy to sites of skeletal involvement. Whether radiotherapy to sites of skeletal involvement can be spared in cases with a negative positron emission tomography after immunochemotherapy should be addressed in appropriately designed prospective trials.

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INTRODUCTION

The addition of the monoclonal anti-CD20 antibody rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy has improved the outcome of patients with diffuse large B-cell lymphoma (DLBCL).[1-3] However, there are only limited data available on the prognostic impact of various sites of extralymphatic involvement in the rituximab era. With respect to skeletal involvement (for review, see Mikhaeel[4]), which accounts for less than 5% of extralymphatic and less than 1% of all non-Hodgkin lymphoma and is most often of the germinal center-like subtype,[5,6] Ostrowski et al[7] suggested classifying bone lymphoma into four groups: (1) solitary bone lymphoma, (2) multifocal bony lesions, (3) distant nodal disease, and (4) cases with visceral disease. However, with more sensitive imaging techniques such as nuclear magnetic resonance and positron emission tomography (PET), the proportion of cases with isolated bone disease is declining,[4] and many institutions treat DLBCL when it manifests itself in a bone the same as other DLBCL. We analyzed the outcome of patients with DLBCL with skeletal involvement treated with and without rituximab within prospective trials of the German High-Grade Non-Hodgkin lymphoma Study Group (DSHNHL) to describe

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clinical characteristics and identify prognostic factors that affect the outcome of these patients when treated with and without rituximab.

PATIENTS AND METHODS

Data were collected from nine prospective trials (Appendix Table A1, online only). Stage was assessed by physical examination; relevant laboratory tests; computed tomography scan of the head and neck, chest, abdomen, and pelvis and sites of bone involvement; bone marrow biopsy; and other investigational procedures depending on clinical symptoms. PET was not used in these trials. Bone lesions were classified as skeletal involvement by the local radiologist if they presented on the computed tomography as lytic destruction or mixed lytic-blastic pattern with or without permeative or moth-eaten structure, as cortical destruction with periosteal reaction, or as bone lesion with presence of additional, adjacent soft tissue mass.[8] Additional magnetic resonance imaging of the respective site and and/or radionucleotide technetium-99 bone scanning was optional. Patients with skeletal involvement only (primary bone lymphoma), with skeletal involvement plus nodal involvement, and/or other extralymphatic were included in this study. In all trials (except for the MegaCHOEP [dose-escalated CHOEP followed by 3 cycles of maximally escalated CHOEP with autologous stem-cell transplantation] phase II trials), additive radiotherapy to extralymphatic sites was recommended (but not mandatory). The dose of radiotherapy was 36 Gy with fractions of 1.8 to 2.0 Gy per day for all patients, except for 19 patients who were treated in the MabThera International Trial (MInT) and received 30 to 47.5 Gy (median, 37.8 Gy).

Persistent radiologic abnormalities after the completion of therapy were common as a result of the slow remodeling process in bones and were defined as treatment failures only if there was evidence of progressive involvement at a given site. Event-free survival (EFS), which was defined as the time from randomization or start of therapy to either disease progression, initiation of salvage therapy, additional (unplanned) treatments, relapse, or death from any cause was the primary end point in all these studies; overall survival (OS) was a secondary end point in these studies and was calculated as time from randomization to death from any cause. EFS and OS were estimated according to the method of Kaplan and Meier. The estimations at 3 years were calculated with 95% CIs. Multivariable analyses were performed using the Cox regression model adjusting for the factors of International Prognostic Index (IPI) or with IPI and bulk. An interaction between rituximab and skeletal involvement was tested using a Cox regression model adjusted for the IPI risk factors. All tests for significance were at the 5% significance level. Statistical analyses were performed with SPSS version 19 (SPSS, Chicago, IL).

RESULTS

Nine consecutive prospective trials of the DSHNHL in patients with newly diagnosed DLBCL were included in this analysis (Appendix Table A1): NHL-B1 (CHOP or CHOEP given every 2 or 3 weeks for young patients [18 to 60 years] with normal LDH),[9] NHL-B2 (CHOP or CHOEP given every 2 or 3 weeks for elderly patients [61 to 75 years] with

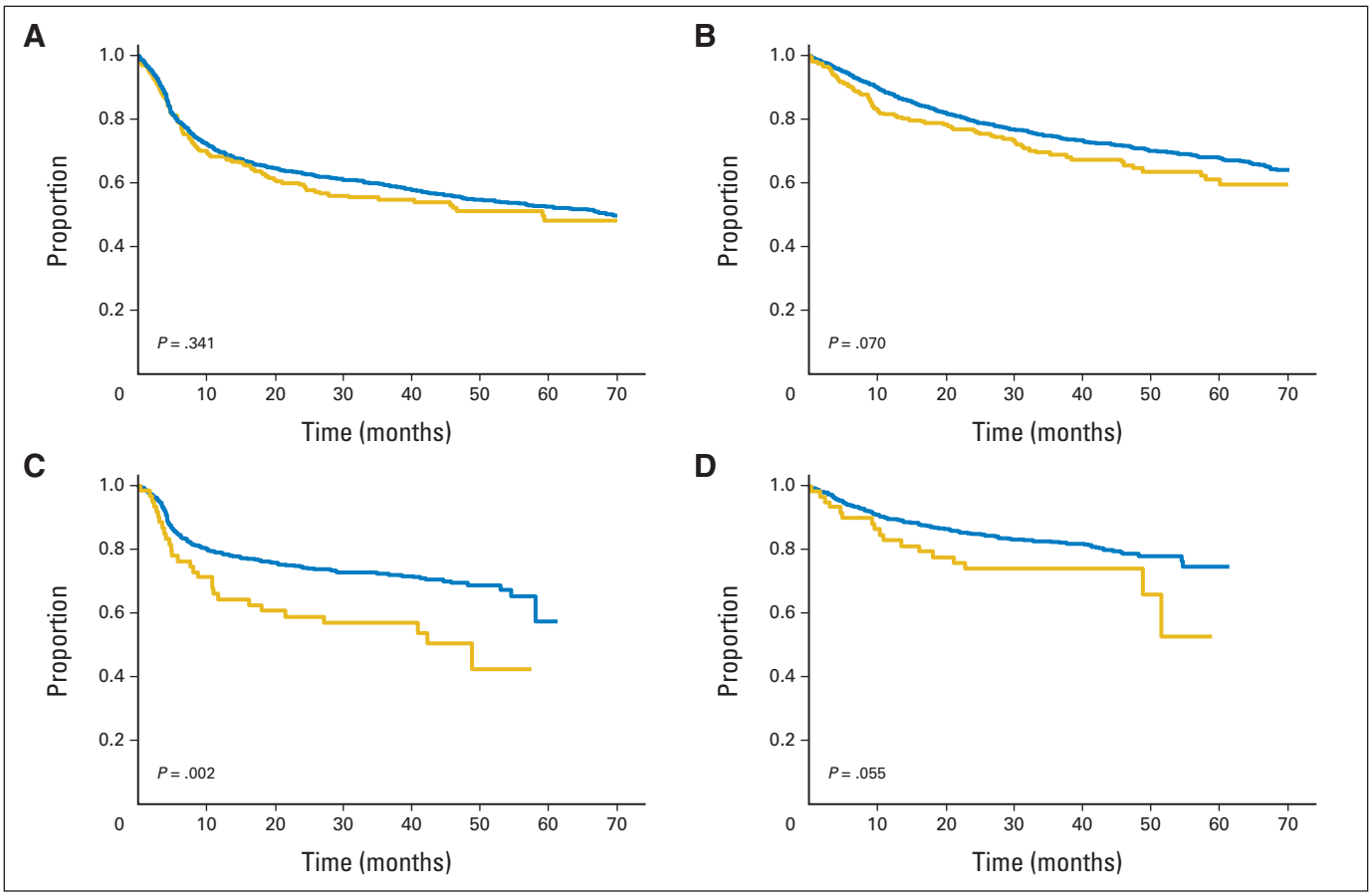

Fig 1. Event-free and overall survival of patients with and without skeletal involvement. In patients treated without rituximab (A, B), there was no difference in outcome between patients with (n = 223) and without (n = 2,583) skeletal involvement. In contrast, in patients treated with rituximab (C, D), event-free survival of 61 patients with skeletal involvement was significantly worse than in 965 patients without skeletal involvement. The 61 patients with skeletal involvement had a worse event-free survival than the 965 patients without skeletal involvement ($P = .002$). Three-year overall survival was 74% versus 82% in favor ($P = .055$) of patients without skeletal involvement. Gold lines represent patients with and blue lines patients without skeletal involvement.

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normal LDH),[10] High-CHOEP phase I/II (dose-escalation study pf CHOEP-14 and CHOEP-21 in young patients with normal LDH),[11] High-CHOEP phase III (CHOEP-21 *v* dose-escalated CHOEP-21 in young patients with normal LDH),[12] two Mega-CHOEP phase II trials,[13,14] MInT,[2] Rituximab With CHOP Over 60 Years (RICOVER-60),[3] and Pegfilgrastim study,[15] covering all IPI risk groups of patients with DLBCL from 18 to 80 years of age. The chemotherapy consisted of CHOP or CHOP plus etoposide (CHOEP) –like regimens given at 2- and 3-week intervals. The Mega-CHOEP studies evaluated dose-escalated CHOP plus etoposide followed by repetitive autologous stem-cell support in young poor-prognosis patients. MInT,[2] which compared CHOP-like chemotherapy regimens with and without rituximab in 823 young (18 to 60 years) patients with good-prognosis DLBL (age-adjusted IPI = 0, 1; except for stage I without bulky disease); the RICOVER-60[3] trial, which compared six cycles versus eight cycles of CHOP-14 with and without rituximab in 1,222 elderly (61 to 80 years of age) patients, and the Pegfilgrastim study,[15] which addressed the same question as the RICOVER-60 trial, evaluated the addition of rituximab to CHOP-like regimens in a randomized fashion. In total, 3,840 patients with aggressive B-cell lymphoma were included in this study. The characteristics of these patients are shown in Appendix Table A2 (online only).

Clinical Presentation

Of the 3,840 patients, 292 (7.6%) had skeletal involvement. Fifty-two patients had only skeletal involvement (or so-called primary bone lymphoma), and 240 patients had skeletal involvement together with additional nodal and/or extralymphatic involvement. Patients with skeletal involvement did not differ with respect to sex and age from patients without skeletal involvement; however, they presented more often with a compromised performance status, more than one extralymphatic site of involvement, advanced stages III/IV, elevated lactate dehydrogenase, and higher IPI score. Patients with bone disease had more often involvement of soft tissues, bone marrow, pleura, liver, and CNS, but more rarely had involvement of the upper GI tract (Appendix Table A3, online only).

Outcome of Patients With and Without Skeletal Involvement

Of the 3,840 patients, 2,814 patients (73.3%) were treated without and 1,026 patients (26.7%) were treated with rituximab. Of the 292 patients with skeletal involvement, 61 (20.9%) were treated with and 231 (79.1%) without rituximab. Skeletal involvement was slightly higher in patients not receiving rituximab (231 of 2,814, or 8.2%) than in patients receiving rituximab (61 of 1,026, or 5.9%). Median time of observation was 41 months in the total group and 44 months in patients with skeletal involvement.

In 2,814 patients treated without rituximab, there was no significant difference between 231 patients with and 2,583 patients without skeletal involvement with respect to 3-year EFS (55% [95% CI, 48% to 61%] *v* 59% [95% CI, 57% to 61%]; $P = .341$) and OS (69% [95% CI, 62% to 75%] *v* 75% [95% CI, 73% to 76%]; $P = .070$). However, in 1,026 patients treated with rituximab, the 61 patients with skeletal involvement had a worse EFS than the 965 patients without skeletal involvement (57% [95% CI, 44% to 70%] *v* 72% [95% CI, 69% to 75%]; $P = .002$). Three-year OS was 74% [95% CI, 63% to 85%] *v* 82% [95% CI, 80% to 85%] in favor ($P = .055$) of patients without skeletal involvement (Fig 1).

Because skeletal involvement was associated with adverse IPI prognostic factors (Appendix Table A2), a multivariable analysis was performed adjusting for the IPI risk factors (Table 1). In the MInT and RICOVER-60 studies, skeletal involvement was not associated with a worse EFS (hazard ratio [HR] = 0.8; $P = .181$) or OS (HR = 0.7; $P = .083$) in 1,022 patients treated without rituximab, but skeletal involvement was associated with a worse outcome in 1,013 patients treated with rituximab ($HR_{EFS} = 1.5, P = .048$; $HR_{OS} = 1.1, P = .828$). A similar picture emerged when all 2,814 patients treated without rituximab and 1,026 patients treated with rituximab were analyzed (Table 1). Rituximab failed to significantly improve the outcome of patients with skeletal involvement in the MInT and RICOVER-60 studies (Fig 2). In a multivariable analysis of the MInT and

Table 1. Multivariable Analysis of Skeletal Involvement

	All Patients Without Rituximab (n = 2,814)			All Patients With Rituximab (n = 1,026)			MInT and RICOVER-60 Patients Without Rituximab (n = 1,022)			MInT and RICOVER-60 Patients With Rituximab (n = 1,013)		
Variable	HR	*P*	95% CI	HR	*P*	95% CI	HR	*P*	95% CI	HR	*P*	95% CI
Event-free survival												
LDH > N	1.5	< .001	1.3 to 1.7	1.7	< .001	1.4 to 2.2	1.6	< .001	1.3 to 1.9	1.6	< .001	1.3 to 2.0
Stage III/IV	1.7	< .001	1.5 to 2.0	1.5	.005	1.1 to 1.9	1.5	< .001	1.2 to 1.9	1.6	.001	1.2 to 2.1
ECOG PS > 1	1.5	< .001	1.3 to 1.8	1.8	.001	1.3 to 2.5	1.8	< .001	1.3 to 2.4	1.7	.002	1.2 to 2.4
Extralymphatic involvement > 1	1.1	.129	1.0 to 1.3	1.0	.821	0.7 to 1.5	1.5	.006	1.1 to 1.9	0.9	.738	0.7 to 1.3
Age > 60 years	1.4	< .001	1.3 to 1.6	1.3	.071	1.0 to 1.7	1.0	.833	0.8 to 1.2	1.4	.035	1.0 to 1.8
Skeletal involvement	0.9	.173	0.7 to 1.1	1.4	.131	0.9 to 2.2	0.8	.181	0.6 to 1.1	1.5	.048	1.0 to 2.4
Overall survival												
LDH > N	2.0	< .001	1.7 to 2.3	2.2	< .001	1.6 to 3.1	2.0	< .001	1.6 to 2.7	2.1	< .001	1.5 to 2.9
Stage III/IV	1.7	< .001	1.4 to 2.0	1.4	.038	1.0 to 2.0	1.3	.061	1.0 to 1.8	1.4	.069	1.0 to 2.0
ECOG PS > 1	1.8	< .001	1.5 to 2.2	1.8	.003	1.2 to 2.5	1.9	< .001	1.3 to 2.6	1.8	.002	1.3 to 2.7
Extralymphatic involvement > 1	1.2	.097	1.0 to 1.4	1.3	.224	0.9 to 1.9	1.9	< .001	1.4 to 2.7	1.2	.473	0.8 to 1.7
Age > 60 years	2.0	< .001	1.7 to 2.4	2.8	< .001	1.8 to 4.4	1.6	.002	1.2 to 2.2	2.8	< .001	1.8 to 4.3
Skeletal involvement	0.9	.328	0.7 to 1.1	1.0	.945	0.6 to 1.8	0.7	.083	0.4 to 1.1	1.1	.828	0.6 to 1.9

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; MInT, MabThera International Trial; RICOVER-60, Rituximab With CHOP Over 60 Years.

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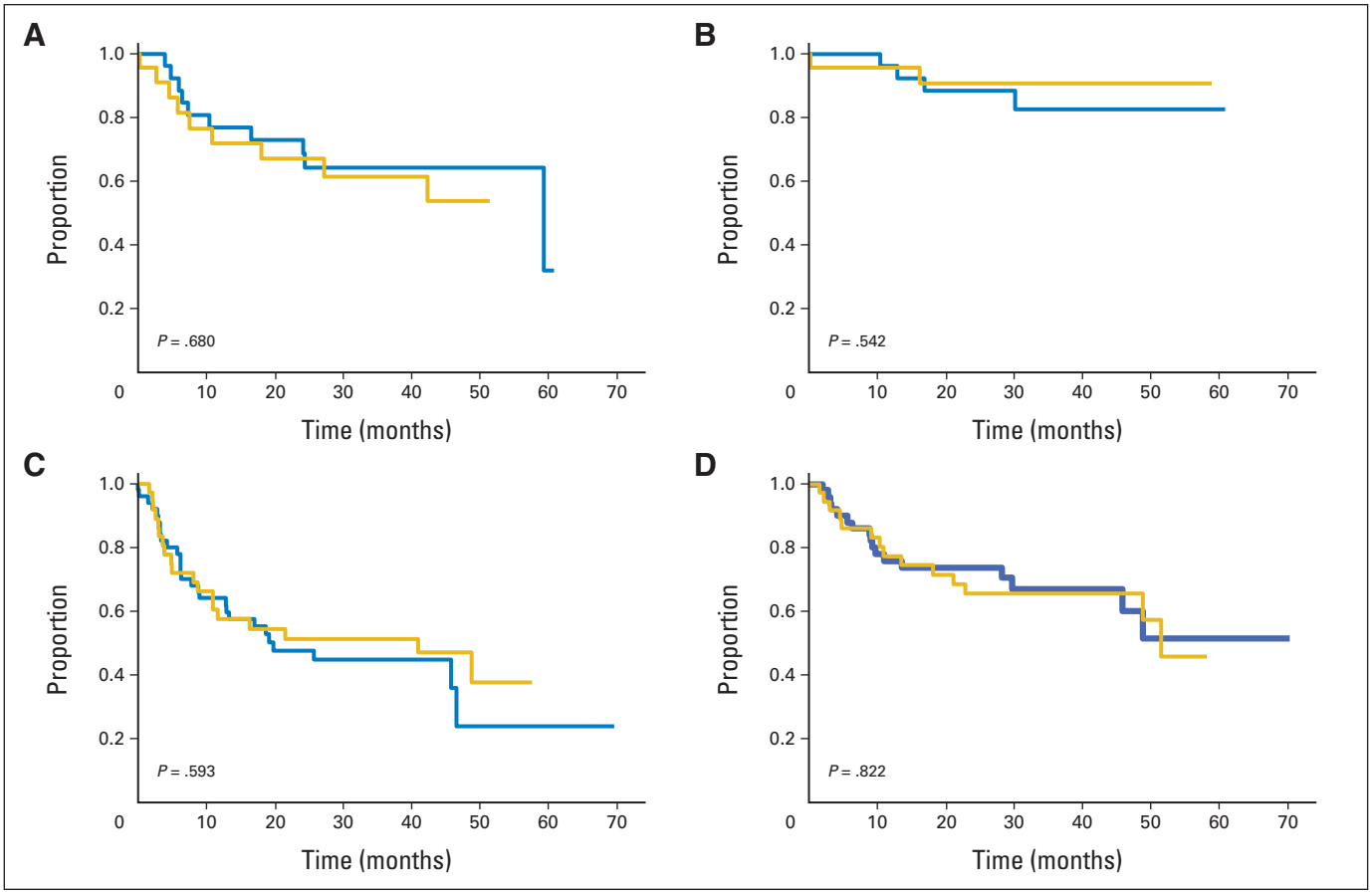

Fig 2. Event-free and overall survival of patients with skeletal involvement treated within the MabThera International Trial (MInT) and the Rituximab With CHOP Over 60 Years (RICOVER-60) study. (A, B) MInT (23 patients treated with and 28 patients without rituximab). (C, D) RICOVER-60 study (36 patients with and 50 patients without rituximab). Gold lines, patients treated with rituximab; blue lines, patients treated without rituximab).

RICOVER-60 studies adjusting for IPI risk factors (Table 2), for patients without skeletal involvement, the addition of rituximab was associated with a significantly improved outcome (EFS_{MInT}: HR = 0.4; $P < .001$; OS_{MInT}: HR = 0.4; $P < .001$; $EFS_{RICOVER-60}$: HR = 0.6; $P < .001$; $OS_{RICOVER-60}$: HR = 0.6, $P <= .001$), but rituximab did not significantly improve the outcome of patients with skeletal involvement (EFS_{MInT}: HR = 1.4, $P = .444$; $OS_{MInT:}$ HR = 0.6, $P = .525$; $EFS_{RICOVER-60}$: HR = 0.8, $P = .449$; $OS_{RICOVER-60}$: HR = 1.0, $P = .935$). Testing for an interaction revealed a relevant interaction term between skeletal involvement and rituximab in a Cox regression model adjusted for the IPI risk factors: HR for MInT and RICOVER-60 was 1.6 ($P = .08$), and HR for all patients in this study was 1.5 ($P = .056$).

Role of Radiotherapy

With the exception of the Mega-CHOEP phase II trials, radiotherapy to extralymphatic sites of lymphoma involvement was recommended (but not mandatory) in all prospective trials included in this study. However, not all institutions participating in the respective studies followed this recommendation, leaving a considerable proportion of patients with skeletal involvement without radiotherapy. This allowed us to study the role of radiotherapy in skeletal involvement. The two Mega-CHOEP phase II trials[13,14] were excluded from this analysis because no radiotherapy was given in these trials. Also, the analysis of the effect of radiotherapy had to be restricted to 161 patients who achieved a complete response (CR), CR unconfirmed, or partial response (PR) after the end of (immuno-)chemotherapy, because patients achieving less than a PR after (immuno-)chemotherapy went off protocol and received salvage chemotherapy. Figure 3 shows the EFS and OS of these 161 patients. The 133 patients who received radiotherapy to sites of skeletal involvement had a significantly better 3-year EFS (75% [95% CI, 67% to 82%] *v* 36% [95% CI, 18% to 55%]; $P < .001$). The respective figures for 3-year OS were 86% (95% CI, 54% to 88%) with radiotherapy versus 71% (95% CI, 54% to 88%; $P = .064$) without.

Because patients who did not receive radiotherapy had worse prognostic factors than those who received radiotherapy (Appendix Table A4, online only), a multivariable analysis adjusting for the IPI risk factors and bulky disease was performed (Table 3). In this multivariable analysis, radiotherapy was confirmed to be associated with a better EFS (HR = 0.3; $P = .001$). The HR for OS for patients receiving radiotherapy was 0.5 ($P = .111$). The beneficial effect of radiotherapy was observed both in limited and advanced stages: for 78 patients with stage I or II disease, the HR was 0.4 ($P = .146$) for EFS and 1.2 ($P = .864$) for OS; for 83 patients with stage III or IV disease, the HR was 0.3 ($P = .001$) for EFS and 0.4 ($P = .059$) for OS, respectively.

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Table 2. Multivariable Analysis of Rituximab in Patients With and Without Skeletal Involvement in the MInT and RICOVER-60 Trials

Factor	With Skeletal Involvement			Without Skeletal Involvement		
	HR	*P*	95% CI	HR	*P*	95% CI
MInT						
No. of patients		51			772	
Event-free survival						
LDH > N	2.6	.171	0.7 to 10.0	1.7	.001	1.3 to 2.4
Stage III/IV	3.0	.088	0.8 to 11.0	1.7	.002	1.2 to 2.4
Chemo + R *v* chemo	1.4	.444	0.6 to 3.7	0.4	< .001	0.3 to 0.6
Overall survival						
LDH > N	1.1	.949	0.2 to 7.5	2.2*	.002	1.3 to 3.5
Stage III/IV	0.7	.767	0.1 to 5.3	1.0*	.952	0.5 to 1.8
Chemo + R *v* chemo	0.6	.525	0.1 to 3.2	0.4*	< .001	0.2 to 0.6
RICOVER-60						
No. of patients		86			1,136	
Event-free survival						
LDH > N	1.9	.059	1.0 to 3.5	1.5	< .001	1.2 to 1.9
Stage III/IV	0.9	.846	0.3 to 3.0	1.6	< .001	1.3 to 1.9
ECOG PS > 1	1.3	.487	0.6 to 2.6	1.8	< .001	1.4 to 2.3
Extralymphatic involvement > 1	1.9	.246	0.7 to 5.3	1.2	.116	1.0 to 1.6
CHOP + R *v* CHOP	0.8	.449	0.4 to 1.5	0.6	< .001	0.5 to 0.7
Overall survival						
LDH > N	1.7	.202	0.8 to 3.7	1.9	< .001	1.5 to 2.4
Stage III/IV	0.8	.785	0.1 to 4.2	1.6	.001	1.2 to 2.0
ECOG PS > 1	1.2	.740	0.5 to 2.7	1.9	< .001	1.5 to 2.5
Extralymphatic involvement > 1	2.4	.228	0.6 to 10.5	1.5	.009	1.1 to 2.0
CHOP + R *v* CHOP	1.0	.935	0.5 to 2.0	0.7	.002	0.6 to 0.9

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; MInT, MabThera International Trial; R, rituximab; RICOVER-60, Rituximab With CHOP Over 60 Years.
*Relative risk.

Toxicity of Radiotherapy

Toxicity of radiotherapy was mild. No National Cancer Institute Common Toxicity Criteria grade 4 toxicities were observed. Leukocytopenia grade 3 was reported in 4.5% of the patients receiving radiotherapy to skeletal sites, and mucositis grade 3 was reported in 8.3% of cases. The leukocyte count 3 months after the end of therapy was 4.9×10^9/L in patients receiving radiotherapy and 5.2×10^9/L in patients receiving only (immuno-)chemotherapy. After a median time of observation of 44 months, second neoplasms occurred in 3.8% of the patients with radiotherapy to skeletal sites, as compared with 3.6% of patients not receiving radiotherapy.

DISCUSSION

To the best of our knowledge, this is the first and largest study of skeletal involvement of DLBCL restricted to prospective trials in the rituximab era. Although the incidence of skeletal involvement might have been underestimated in this study because staging did not include PET scanning,[4] the number of patients with skeletal involvement is still small, limiting the number of sensible subgroup analyses, and demonstrates that randomized trials for this subgroup of DLBCL are hardly feasible, leaving a retrospective analysis of unselected prospective trials the best compromise to get answers to the questions that we addressed in this study. We tried to avoid selection biases by including all previously published trials of the DSHNHL covering all subgroups of DLBCL patients between 18 and 80 years of age. Although multiple chemotherapy regimens were used in these trials, including the recently published comparison of dose-escalated R-Mega-CHOEP and R-CHOEP-14,[16] their efficacy was similar and unlikely to influence the results of our analysis.

We found no difference in outcome of patients with and without skeletal involvement when treated without rituximab, confirming the results of previous reports of patients treated with CHOP without rituximab.[17,18] In contrast, in patients treated with rituximab, skeletal involvement evolved as a risk factor because the addition of rituximab significantly improved the outcome of the patients without skeletal involvement, but failed to significantly improve the results of both young and elderly patients with skeletal disease in MInT[2] and the RICOVER-60[19] study, respectively, but failed to significantly improve the results of both young and elderly patients with skeletal disease in MInT[2] and the RICOVER-60[19] study, respectively, the two largest trials to date that randomly evaluated the role of rituximab. That our results are in contrast to previous reports[18,20] might be explained by the smaller number of patients included in the respective studies and by the fact that these analyses were not restricted to prospective and randomized trials. The reason for the relevant interaction of rituximab and skeletal involvement (HR = 1.6, $P = .080$ for MInT and RICOVER-60 patients; HR = 1.5, $P = .056$ for all patients included in this study) remains unclear. Because young patients received conventional CHOP-21–like chemotherapy in the MInT trial and elderly patients received dose-dense CHOP-14 in the RICOVER-60 trial, rituximab exposure time and age cannot serve as an explanation for the lack of rituximab efficacy in patients with skeletal involvement. Whether access of rituximab to sites of skeletal involvement is compromised and/or the commonly used dose and schedule of rituximab, which seems to be suboptimal for subpopulations with a fast rituximab clearance (eg, elderly male patients),[21] is also insufficient for skeletal involvement, or whether skeletal involvement by DLBCL represents a biologic subtype that is partially resistant to rituximab can only be speculated on. That such a subtype would correlate with the GC- versus non-GC type is unlikely, because in the RICOVER study, the only study in which such an analysis was done, the fraction of patients with the non-GC type was similar in patients without (175 of 330, or 53%) and with skeletal involvement (11 of 22, or 50%; $P = .783$).[22]

Our observation of a lack of a significant effect of rituximab on outcome of patients with skeletal involvement in MInT and RICOVER-60 is in contrast to a retrospective register study that included 103 cases with DLBCL[20] recruited over a period of more than 20 years. However, the results of this small retrospective register study can hardly be compared with the results of MInT and the RICOVER-60 trial, the two largest trials to date that have

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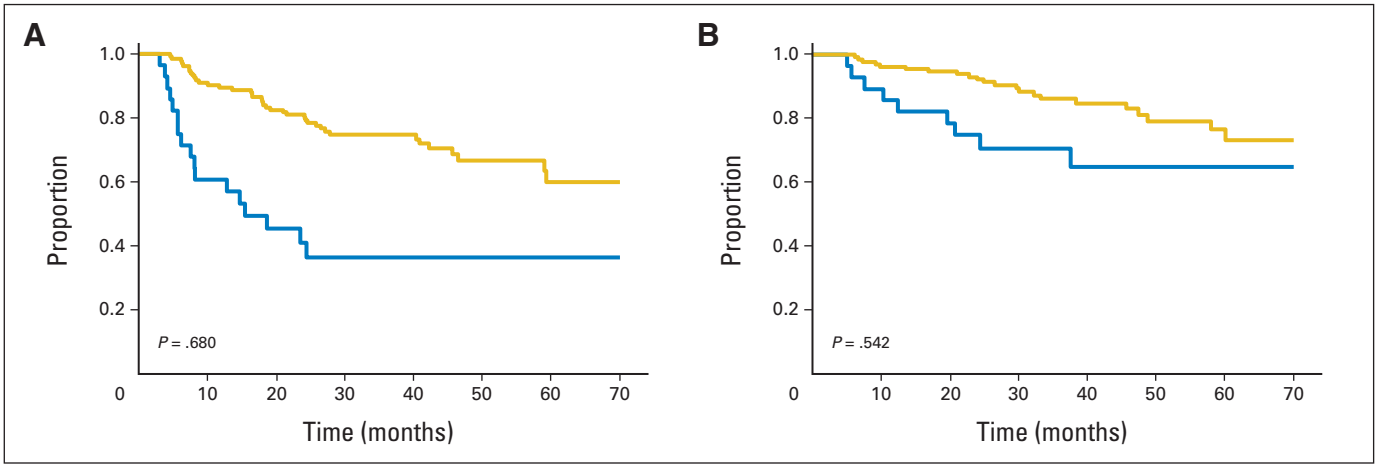

Fig 3. (A) Event-free and (B) overall survival of patients with diffuse large B-cell lymphoma with skeletal involvement treated with and without radiotherapy to sites of skeletal involvement. Gold lines represent patients treated with (n = 133) and blue lines represent patients treated without (n = 28) radiotherapy to skeletal sites.

addressed the role of rituximab in a prospective and randomized fashion.

The second major finding of our study is the superior outcome of patients with skeletal disease who received additive radiotherapy to these sites. This analysis had to be restricted to the positive selection of patients who achieved a CR, CR unconfirmed, or PR (because all other patients received salvage therapy), and therefore, the 3-year EFS and OS rates of these patients are better than for the whole population. Even though the dose of radiotherapy ranged from 30 to 40 Gy in MInT, more than 90% of all patients included in our analysis had received a dose of 36 Gy with 5 × 1.8 Gy per week, representing a rather homogeneously irradiated population.

Several studies have shown that combined modality treatment consisting of chemotherapy plus radiotherapy is superior to radiotherapy alone.[19,23-28] However, whether combined chemoradiotherapy is superior to chemotherapy alone has not been settled, and many cooperative groups have abandoned radiotherapy in the rituximab era. Although our observation of a benefit of adding radiotherapy to (immuno-)chemotherapy in DLBCL with skeletal involvement was not made in a randomized study addressing the role of radiotherapy to skeletal involvement of DLBCL, it is supported by the results of multivariable analyses, which were not performed in previously reported studies[20,23,25,26,29-32] addressing this question. A comparison of results obtained from two studies in young patients with one risk factor according to the age-adjusted IPI[33,34] was a first clue in the rituximab era that radiotherapy may have a value at least in some subpopulations of DLBCL (in that case, bulky disease) because results with six cycles of R-CHOP-21 were better in MInT,[33] in which patients had received radiotherapy to bulky disease, compared with eight cycles of R-CHOP-21 in the LNH03-2B[34] study, in which no radiotherapy was given. These observations underline the need of a re-evaluation of the impact of additive radiotherapy in the rituximab era. Although patients not receiving radiotherapy were older and had a worse prognostic profile according the IPI, radiotherapy to sites of skeletal involvement retained its independent prognostic power in the multivariable analysis adjusted for the IPI risk factors (Table 3), with an HR of 0.3 ($P = .001$) for EFS and 0.5 ($P = .111$) for OS. With the caveat of small numbers, the beneficial effect of radiotherapy was observed both in the roughly 20% of patients with extensive (ie, combined supra- and infradiaphragmatic) skeletal involvement and in those with more limited skeletal involvement (data not shown). In addition, 70% of relapses in patients treated in MInT and RICOVER-60 occurred exclusively outside the radiotherapy field, 20% occurred within and outside the field, and only 10% occurred exclusively in previously irradiated sites. Moreover, of patients with skeletal involvement who experienced treatment failure and for whom the type of salvage therapy is known, one third received radiotherapy as part of their salvage therapy. Of these patients, one third received radiotherapy as monotherapy, one third in combination with conventional chemotherapy, and one third in combination with high-dose chemotherapy followed by stem-cell transplantation, partially explaining why the differences in EFS did not translate into differences in OS.

Although the observation time of our study is too short to exclude an increase in second neoplasms, the mild acute toxicity of radiotherapy to skeletal sites with total doses not exceeding 40 Gy should not argue against radiotherapy. PET scans have a high sensitivity for the detection of DLBCL in the bone,[35] but a low

Table 3. Multivariable Analysis of Additive Radiotherapy in Patients With Skeletal Involvement

Variable	EFS (n = 161)			OS (n = 161)		
	HR	*P*	95% CI	HR	*P*	95% CI
LDH > N	1.9	.032	1.1 to 3.5	1.4	.413	0.6 to 3.1
Stage III/IV	2.4	.015	1.2 to 5.0	2.2	.110	0.8 to 6.0
ECOG PS > 1	0.6	.211	0.3 to 1.3	0.8	.680	0.3 to 2.0
Extralymphatic involvement > 1	0.8	.609	0.4 to 1.7	0.8	.683	0.3 to 2.2
Age > 60 years	1.0	.987	0.5 to 1.9	1.9	.147	0.8 to 4.5
Bulk	1.6	.133	0.9 to 2.9	2.8	.010	1.3 to 6.3
Additive radiotherapy	0.3	.001	0.2 to 0.6	0.5	.111	0.2 to 1.2

NOTE. Only 161 patients in complete response, complete response unconfirmed, or partial response after the end of (immuno)chemo therapy are included in this analysis. Patients achieving less than partial response received salvage treatment and were excluded from this analysis.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival.

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predictive value of residual positivity involving bone when performed after the completion of immunochemotherapy,[36] because bone remodeling and inflammation may contribute to false-positive cases. Therefore, whether PET scans can identify those patients with bone lymphoma who can be spared from radiotherapy remains to be shown in appropriately designed trials addressing this question.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Gerhard Held, Samira Zeynalova, Christian Rübe, Norbert Schmitz, Michael Pfreundschuh
Administrative support: Norbert Schmitz
Provision of study materials or patients: Bertram Glass
Collection and assembly of data: Gerhard Held, Niels Murawski, Marita Ziepert, Barbara Kempf, Andreas Viardot, Martin Dreyling, Michael Hallek, Mathias Witzens-Harig, Jochen Fleckenstein, Carsten Zwick, Bertram Glass, Norbert Schmitz, Michael Pfreundschuh
Data analysis and interpretation: Gerhard Held, Samira Zeynalova, Marita Ziepert, Mathias Witzens-Harig, Jochen Fleckenstein, Michael Pfreundschuh
Manuscript writing: All authors
Final approval of manuscript: All authors

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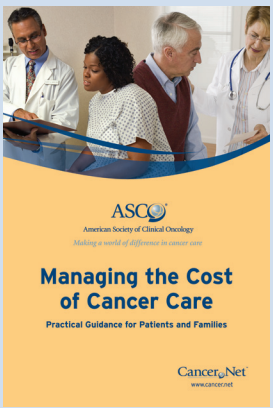

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Appendix

Table A1. Prospective Trials Included in This Study

Study	Study Population	Treatment	Patients With Skeletal Involvement	Patients Without Skeletal Involvement	Total Patients
NHL-B1[9]	18-60 years, LDH < ULN	CHOP-21, CHOEP-21, CHOP-14, CHOEP-14	56	624	710
NHL-B2[10]	61-75 years, all stages	As in NHL-B2	61	628	689
High-CHOEP-Phase I/II[11]	18-60 years, LDH < ULN	Dose-escalating CHOEP-21 Dose-escalating CHOEP-14	10	109	119
High-CHOEP-Phase III[12]	18-60 years, LDH < ULN	Escalated CHOEP-21 Standard CHEOP-21	18	371	389
Mega-CHOEP-Phase 2[13]	18-60 years, LDH > ULN	4 × Mega-CHOEP with 3 × ASCT	6	35	41
Mega-CHOEP-Phase 2[14]	18-60 years, LDH > ULN	4 × Mega-CHOEP with 3 × ASCT	12	98	110
MInT[2]	18-60 years, aaIPI = 0, 1 (excluding nonbulky stage I)	CHOP-like chemotherapy With and without rituximab	51	772	823
RICOVER-60[3]	61-80 years, all stages	6 × CHOP-14, 8 ×CHOP-14 6 × R-CHOP-14 + 2R: 8 × CHOP-14	86	1,136	1,222
Pegfilgrastim [15]	61-80 years, all stages	As in RICOVER, with pegfilgrastim day 2 *v* Pegfilgrastim day 4	12	91	103
With rituximab			61	965	1,026
Without rituximab			231	2,583	2,814
Total			292	3,548	3,840

Abbreviations: aaIPI, age-adjusted International Prognostic Index; ASCT, autologous stem-cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOEP, CHOP plus etoposide; High-CHOEP Phase I/II, dose-escalation study of CHOEP-21 (CHOEP every 3 weeks) and CHOEP-14 (CHOEP every 2 weeks); High-CHOEP Phase III, dose-escalated CHOEP-21 *v* standard CHOEP-21; LDH, lactate dehydrogenase; Mega-CHOEP, dose-escalation of CHOEP with autologous stem-cell transplantation; MInT, MabThera International Trial; R-CHOP, rituximab plus CHOP; RICOVER-60, Rituximab With CHOP Over 60 Years; ULN, upper limit of normal.

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Table A2. Characteristics of Patients Included in This Study

Characteristic	All Patients With Aggressive B-Cell Lymphoma (n = 3,840)					Patients Without Rituximab (n = 2,814)					Patients With Rituximab (n = 1,026)				
	With Skeletal Involvement (n = 292)		Without Skeletal Involvement (n = 3,548)			With Skeletal Involvement (n = 231)		Without Skeletal Involvement (n = 2,583)			With Skeletal Involvement (n = 61)		Without Skeletal Involvement (n = 965)		
	No.	%	No.	%	*P*	No.	%	No.	%	*P*	No.	%	No.	%	*P*
Sex															
Male	158	54.1	1,973	55.6		126	54.5	1,429	55.3		32	52.5	544	56.4	
Female	134	45.9	1,575	44.4	.620	105	45.5	1,154	44.7	.820	29	47.5	421	43.6	.550
Age, years															
Median	61		60		.251	61		58			64		64		
Range	19-79		18-80			22-79		18-80			19-79		18-80		
> 60	156	53.4	1,750	49.3	.178	116	50.2	1,158	44.8	.115	40	65.6	592	61.3	.510
ECOG PS > 1	62	21.2	338	9.5	< .001	50	21.6	255	9.9	< .001	12	19.7	83	8.6	.004
Stage III/IV	176	60.3	1,399	39.4	< .001	135	58.4	1,017	39.4	< .001	41	67.2	382	39.6	< .001
LDH > N	127	43.5	1,304	36.8	.022	99	42.9	893	34.6	.012	28	45.9	411	42.6	.612
Extralymphatic involvement > 1	179	61.3	456	12.9	< .001	139	60.2	351	13.6	< .001	40	65.6	105	10.9	< .001
Bulk	124	42.5	1,422	40.1	.498	101	43.7	1,012	39.2	.177	23	37.7	410	42.5	.463
IPI															
0, 1	94	32.2	2,121	59.8		78	33.8	1,575	61.0		16	26.2	546	56.6	
2	64	21.9	665	18.7		50	21.6	477	18.5		14	23.0	188	19.5	
3	55	18.8	478	13.5		43	18.6	333	12.9		12	19.7	145	15.0	
4, 5	79	27.1	283	8.0	< .001	60	26.0	197	7.6	< .001	19	31.1	86	8.9	< .001
Lymphoblastic precursor B cell*	2	0.7	4	0.1		2	0.9	3	0.1		0	0.0	1	0.1	
Diffuse large B cell*	246	82.3	2,875	81.0		193	83.5	2,050	79.4		53	86.9	825	85.5	
Centroblastic	144	49.4	1,546	43.6		123	53.2	1,182	45.7		21	34.4	364	37.7	
Immunoblastic	14	4.8	211	5.9		13	5.6	175	6.8		1	1.6	36	3.7	
Plasmablastic	1	0.3	12	0.3		0	0.0	4	0.2		1	1.6	8	0.8	
Anaplastic large cell	7	2.4	73	2.1		6	2.6	50	1.9		1	1.6	23	2.4	
T-cell rich B cell	2	0.7	84	2.4		2	0.9	63	2.4	0	0.0	21	2.2		
Prim. mediastinal B cell	9	3.1	180	5.1		7	3.0	135	5.2		2	3.3	45	4.7	
NOS	69	23.6	769	21.6		42	18.2	441	17.1		27	44.3	328	34.0	
												0.0			
Primary effusion lymphoma*	0	0.0	1	< 0.1		0	0.0	1	< 0.1		0	0	0.0		
Follicular lymphoma grade IIIb*	4	1.4	175	4.9		4	1.7	139	5.4		0	0.0	36	3.7	
Follicular lymphoma grade IIIb* + DLBCL*	6	2.1	138	3.9		3	1.3	104	4.0		3	4.9	34	3.5	
Burkitt lymphoma*	0	0.0	22	0.6		0	0.0	14	0.5		0	0.0	8	0.8	
Burkitt-like*	4	1.4	44	1.2		4	1.7	36	1.4		0	0.0	8	0.8	
Mantle cell lymphoma (blastic)*	0	0.0	39	1.1		0	0.0	27	1.0		0	0.0	12	1.2	
Aggressive marginal zone lymphoma	0	0.0	38	1.1		0	0.0	27	1.0		0	0.0	11	1.1	
NOS	15	5.1	103	2.9		12	5.2	91	3.5		3	4.9	12	1.2	
B-cell (unclassified, technology insufficient)	15	5.1	109	3.1		13	5.6	91	3.5		2	3.3	18	1.9	

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NOS, not otherwise specified.

*As defined by reference pathology.

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Table A3. Clinical Presentation of Patients With and Without Skeletal Involvement

Site of Involvement	With Skeletal Involvement (n = 292) No.	%	Without Skeletal Involvement (n = 3,548) No.	%	*P*
Lung	20	6.8	176	5.0	.159
Liver	21	7.2	119	3.4	.001
Bone marrow	49	16.8	208	5.9	< .001
Pleura	23	7.9	114	3.2	< .001
Pericardium	6	2.1	51	1.4	.443
CNS	12	4.1	20	0.6	< .001
Stomach/intestine	12	4.1	387	10.9	< .001
Orbita	4	1.4	26	0.7	.283
Paranasal sinuses	10	3.4	80	2.3	.204
Main nasal cavity	2	0.7	36	1.0	1.000
Mouth region	4	1.4	95	2.7	.175
Tongue	0	0.0	26	0.7	.258
Salivary glands	1	0.3	52	1.5	.184
Thyroid gland	2	0.7	52	1.5	.434
Mammary gland	2	0.7	55	1.6	.318
Peritoneum	1	0.3	18	0.5	1.000
Pancreas	1	0.3	57	1.6	.127
Kidney	6	2.1	73	2.1	.998
Adrenal gland	2	0.7	46	1.3	.581
Urinary bladder	0	0.0	26	0.7	.258
Testes	2	0.7	84	2.4	.062
Ovary	1	0.3	22	0.6	1.000
Uterus	0	0.0	19	0.5	.393
Skin	8	2.7	70	2.0	.372
Soft tissues	67	22.9	193	5.4	< .001
Ascites	1	0.3	12	0.3	1.000

Table A4. Characteristics of Patients With Skeletal Involvement Treated With and Without Radiotherapy to Sites of Skeletal Involvement and Achieving a CR, CRu, or PR (n = 161)

Characteristic	With Radiotherapy (n = 133) No.	%	Without Radiotherapy (n = 28) No.	%	*P*
Sex					
Male	82	61.7	10	35.7	.012
Female	51	38.3	18	64.3	
Age > 60 years	58	43.6	22	78.6	.001
ECOG PS > 1	21	15.8	6	21.4	.577
Stage III/IV	63	47.4	20	71.4	.021
LDH > N	41	30.8	12	42.9	.218
Extralymphatic involvement > 1	67	50.4	18	64.3	.180
Bulk	45	33.8	5	17.9	.097
IPI					
0, 1	61	45.9	8	28.6	
2	33	24.8	3	10.7	.017
3	18	13.5	7	25.0	
4, 5	21	15.8	10	35.7	

Abbreviations: CR, complete response; CRu, CR unconfirmed; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PR, partial response.

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