Diffuse large B-cell lymphoma involving osseous sites: utility of response assessment by PET/CT and good long-term outcomes

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Abstract

Osseous involvement by diffuse large B-cell lymphoma (DLBCL-bone) is a heterogeneous disease. There is limited data regarding response assessment by positron emission tomography with fluorodeoxyglucose, which may demonstrate residual avidity despite a complete response. We analyzed clinical data of patients with newly diagnosed DLBCL and identified all cases with DLBCL-bone. End of treatment scans were reviewed by two independent experts classifying osseous lesions into Deauville (DV) ≤3; DV ≥4, or reactive uptake in the bone marrow (M), site of fracture (F) or surgery (S). We compared outcomes of DLBCL-bone to other extranodal sites (EN) matched on International Prognotic Index features and regimen. Of 1,860 patients with DLBCL (bone 16%; EN 45%; nodal 39%), 41% had localized disease and 59% advanced. Only 9% (n=27) of patients with initial bone involvement had residual fluorodeoxyglucose avidity at the osseous site. In half of these cases, the uptake was attributed to F/S/M, and of the remaining 13, only two were truly refractory (both with persistent disease at other sites). Overall survival and progression-free survival (PFS) were found to be similar for early-stage nodal DLBCL and DLBCL-bone, but inferior in EN-DLBCL. Advanced-stage disease involving the bone had a similar 5-year PFS to nodal disease and EN-DLBCL. After matching for International Prognotic Index and treatment regiments, PFS between bone and other EN sites was similar. Osseous involvement in DLBCL does not portend a worse prognosis. End of treatment DV ≥4 can be expected in 5-10% of cases, but in the absence of other signs of refractory disease, may be followed expectantly.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma,[1] involving extranodal sites (EN) in 30% to 60% of the patients.[2] Approximately 7% to 21% of DLBCL present with osseous lesions.[3] Standard of care treatment for DLBCL is chemoimmunotherapy, followed by response evaluation with functional imaging and consideration of consolidation radiation therapy (RT), particularly for localized disease.[4-7]

Several retrospective studies evaluated the clinical course of advanced DLBCL with osseous involvement (i.e., stage IV), of early-stage osseous disease (stage I/II-E) and disease confined to bony sites (primary bone lymphoma).[8-13] Notably, in nearly all studies, data was limited to bone involvement as identified by computed tomography (CT) with minimal information about the rate of cortical bone involvement by positron emission tomography (PET) in the absence of CT findings. When evaluated by CT, osseous involvement can be seen in 7.6% in advanced-stage disease and has been associated with a reduced event-free survival.[8] In localized DLBCL, osseous involvement can be seen in 3% when evaluated by CT, yet we have recently demonstrated up to 21% of patients may have evidence of involvement by PET.[14] In that study, any EN involvement (i.e., stage I/II-E) was associated with a poorer prognosis, however, the analysis did not include a dedicated evaluation for lymphoma involving osseous sites. More recently, analysis of localized

DLBCL treated on three consecutive Southwestern Oncology Group studies (S0014, S0313, S1001; *clinicaltrials gov. Identifier: NCT00005089, NCT00070018, NCT01359592*) has been published.[15] Their results contrast with those from Bobillo *et al*.[14] and do not support EN disease as an adverse prognostic factor for patients with localized DLBCL. In that regard, primary bone lymphoma, historically has been shown to carry an excellent prognosis.[10-13] Interestingly, better prognosis has also been demonstrated for multi-focal (stage IV) primary bone lymphoma compared to disease involving both nodal and osseous sites.[11 16]
Possibly contributing to the concerns associated with osseous presentation, is the limited data regarding response assessment by PET with fluorodeoxyglucose (FDG), which may demonstrate residual avidity despite a complete response. Of note that the Deauville (DV) criteria were devised based on data from nodal disease, and it is unclear whether they can be applied to EN sites.[17-19] Osseous sites, for example, may be associated with residual uptake at the end of treatment including false-positive uptake due to fractures, reactive bone marrow uptake, or bone reconstruction.[20,21]
In the present work we aimed to evaluate clinical and PET features of DLBCL involving the bone and to assess their association with treatment outcomes and disease course.

Methods

Following institutional review board approval, we reviewed all adult patients (age ≥18 years) with newly diagnosed DLBCL treated with the combination of rituximab, cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP) and R-CHOP-like chemotherapy at Memorial Sloan Kettering Cancer Center (MSKCC) between 2000 and 2015. All patients underwent a PET-CT scan at diagnosis. We evaluated response assessment by PET-CT in patients with bone involvement and compared treatment outcomes to patients with DLBCL involving other sites of EN disease and to patients with disease limited to nodal sites.
Patient data were collected from our institutional lymphoma database. Medical and pathology records were evaluated for clinical characteristics, pathologic and radiologic data, treatment history and outcomes. Treatment was considered to have occurred if at least one cycle of the chemo-immunotherapy was administered.
Cortical bone involvement was identified by review of all imaging reports pretreatment and at end of treatment (EOT) by two independent reviewers. Patients with isolated involvement of the bone marrow without involvement of the cortical bone were not considered DLBCL-bone for this analysis. Whenever a high focal bone uptake was noted without CT abnormalities, it was considered as positive for bone lesions.[22] EOT scans of patients with any residual FDG avidity above the liver mean standardized uptake value (SUV) at any initially involved osseous sites were referred for further review by two independent and blinded radiologists specialized in nuclear medicine. EOT response was classified according to the DV criteria as DV ≤3 (uptake similar or lower than liver); DV ≥4 (uptake greater than liver) with a separate designation for superimposed uptake due to reactive bone marrow (M), site of fracture (F) or site of surgery (S).[19] Cases with disagreement between the two radiologists were evaluated by a third reviewer and resolved by consensus. Overall response to treatment was based on the Lugano criteria.[23]
We grouped patients into osseous, other EN and strictly nodal disease groups. We compared baseline characteristics, response to treatment and survival between the groups separately for localized disease (i.e., stage I/II nodal; I/II-E with osseous involvement; I/II-E with non-osseous EN involvement) and advanced stage disease (i.e., stage III; stage IV osseous; stage IV non-osseous). Finally, we compared survival between the patients with osseous involvement and a cohort of patients with other EN sites matched 1:2 on International Prognostic Index (IPI) features (stage, number of EN sites, age, lactate dehydrogenase [LDH], performance status, cell of origin was determined by the Hans algorithm)[24] and on treatment regimen.
Baseline characteristics between the groups were compared using the Fisher exact test for categorical variables and the Kruskal-Wallis test for numeric variables. Categorical data are reported as percent (number) and numeric data as median (interquartile range [IQR]). Overall survival (OS) was defined as the time from initiation of treatment to death of any cause censoring at date of last follow-up. Progression-free survival (PFS) was defined as time from initiation of treatment until progression of disease or death of any cause, censoring at date of last follow-up. Time-to-event statistics were estimated using the Kaplan-Meier method, and compared between the groups using the log-rank test. All analyses were performed using R (R version 3.6.3, Austria).

Results

Patients

We analyzed data of 1,860 patients with DLBCL receiving R-CHOP or R-CHOP-like treatment between 2000 and 2015. Within this population, 39% (n=732) had purely nodal disease, and 61% (n=1,128) had EN involvement. Bone was the most commonly involved EN site with 300 patients having at least one osseous lesion (27% of all EN and 16% of the entire cohort). The most commonly involved other EN sites were lungs 16% (n=180), stomach 13% (n=143), gastro-intestinal tract 12% (n=130), muscle and non-nodal soft tissue 11% (n=126), liver 10% (n=116), bone marrow 9% (n=103), kidney/adrenal 7% (n=83), skin/subcutaneous 6% (n=63), breast 4% (n=46), pancreas 4% (n=45), testis 4% (n=45), with other sites being less frequent. Concurrent systemic and central nervous system involvement was found in 2% (n=21). In the entire cohort, 41% (n=766) had localized dis-

ease and 59% (n=1,094) advanced stage.
Most patients received frontline chemotherapy with R-CHOP (70%, n=1306), R-EPOCH (13%, n=232) or a regimen of four cycles of R-CHOP followed by three cycles of R-ICE (ifosfamide, carboplatin, etoposide) (17%, n=322).[25,26] Progression/relapse (POD) after frontline chemotherapy were recorded in 20% (n=374) and all-cause deaths in 25% (n=460). Baseline characteristics for limited and advanced stage are presented in Tables 1 and 2, respectively.

Limited stage

Of the 766 patients with limited stage disease 5.5% (n=42) had DLBCL-bone and 35% (n=271) had EN-DLBCL (Table 1). Patients with DLBCL-bone were significantly younger (age 46 stage I/II-bone *versus* 62 I/II-EN *versus* 55 I/II-nodal; *P*<0.001) with 38% of them (n=16) below the age of 40 at diagnosis. DLBCL-bone was further characterized by a higher rate of germinal center B-cell (GCB) cell of origin (64% stage I/II-bone *vs*. 36% I/II-EN *vs*. 45% I/II-nodal; *P*=0.008). Of note, none of the stageI-II DLBCL localized to the bone showed a transformed histology.

Advanced stage

Of the 1,094 patients with advanced stage DLBCL 26% (n=279) had a purely nodal disease (stage III), 24% (n=258) had DLBCL-bone and 51% (n=557) EN-DLBCL (Table 2). Most DLBCL-bone patients (64%) had involvement of an additional EN site, and these patients were managed more aggressively with 48% (n=125) treated with R-EPOCH or R-CHOP/RICE rather than RCHOP as compared to 33% (n=183) and 31% (n=85) of patients with EN and nodal disease, respectively (*P*<0.001).

Positron emission tomography response assessment

Most patient demonstrated a complete metabolic response (CMR) by PET at the site of osseous involvement (DV ≤3 in 91%, n=273). Positive EOT PET (DV ≥4) had low predictive value for residual disease. In half of the PET-positive cases (14/27), after re-review by our three blinded nuclear medicine physicians, the uptake was attributed to local fracture, surgery, or background marrow uptake (F/S/M). The remaining 13 cases (4%) were truly suspicious for residual osseous disease, but only two patients had refractory disease, both with additional extra-osseous sites. One patient was consolidated with radiation as part of the preplanned treatment. Ten patients did not receive further treatment, and four of them had repeat biopsies (3 osseous site; 1 adjacent LN) which were negative. Two of these ten patients subsequently relapsed, but only one had recurrent disease at the initial site of osseous involvement (35 months after initial treatment). With a median follow-up of over 5 years, 25% (n=76) of patients with osseous in-

Table 1. Limited stage (I/II) diffuse large B-cell lymphoma - baseline characteristics.

Variable, total N=766	I-II Nodal N=453	I-II EN-bone N=42	I-II EN-other N=271	*P* overall	*P* bone *vs*. EN
Age in years, median (IQR)	55.0 (41.0-68.0)	46.0 (31.0-65.5)	62.0 (51.0-72.0)	<0.001	<0.001
Sex F, N (%)	228 (50.3)	19 (45.2)	142 (52.4)	0.658	0.411
PS ECOG ≥2, N (%)	35 (7.73)	2 (4.76)	16 (5.90)	0.639	1.000
IPI 3-5, N eval.=740, N (%)	12 (2.75)	0 (0.00)	5 (1.90)	0.389	0.172
Cell of origin (Hans alg.), N (%) GCB non-GCB (available for 563 pts)	 196 (43.3) 144 (31.8)	 27 (64.3) 9 (21.4)	 98 (36.2) 89 (32.8)	 0.008	 0.001
Transformed, N (%) Bulky ≥10 cm, N eval.=706, N (%) LDH >ULN, N eval.=715, N (%)	53 (11.7) 117 (26.5) 193 (45.8)	0 (0.00) 5 (14.7) 14 (35.0)	19 (7.01) 16 (6.96) 70 (27.6)	0.006 <0.001 <0.001	0.088 0.177 0.469
Treatment, N (%) R-CHOP R-EPOCH/R-CHOP-R-ICE	 325 (71.7) 128 (28.2)	 38 (90.5) 4 (9.52)	 242 (89.3) 29 (10.7)	 <0.001	 1.000
N of cycles (%) ≥5 3-4 Incomplete treatment	 311 (68.7) 132 (29.1) 10 (2.21)	 23 (54.8) 19 (45.2) 0 (0.00)	 139 (51.3) 127 (46.9) 5 (1.85)	 <0.001	 1.000
Radiation therapy, N (%)	143 (31.6)	27 (64.3)	127 (46.8)*	<0.001	0.316

EN: extranodal; IQR: interquartile range; F: female; LDH: lactate dehydrogenase; ULN: upper limt of normal; eval: evaluated; R-CHOP: rituximab, cyclophosphamide, adriamycin, vincristine and prednisone; R-EPOCH: rituximab, etoposide, cyclophosphamide, adriamycin, vincristine and prednisone; R-ICE: rituximab ifosfamide, carboplatin, etoposide; PS ECOG: performance status by Eastern Cooperative Oncology Group; IPI: International Prognostic Index; Hans alg.: Hans algorithm; GCB: germinal center B-cell derived; pts: patients. *Excluding 21 cases with radiation therapy to contralateral testis.

volvement experienced treatment failure or relapse, but only in 6% did the relapse involve the initial osseous site (Figure 1). PFS among patients with DV ≤3 and ≥4, or with F/S/M avidity was similar (Figure 2).

Survival of limited and advanced stage disease

OS at 5 years (5y-OS) was similar for early-stage nodal DLBCL and DLBCL-bone and inferior in EN-DLBCL (5y-OS 93% and 95% *vs*. 88%, respectively; *P*=0.02). PFS at 5 years (5y-PFS) in patients with nodal DLBCL was superior to that of early-stage bone DLBCL and EN-DLBCL (5y-PFS 92% for nodal DLBCL, 84% for bone DLBCL and 84% for EN-DLBCL; *P*=0.03). Of note, none of the 34 patients with stage I-bone ever relapsed, translating to a 5y-PFS of 97% (1 late death; compared to 93% for nodal DLBCL and 84% for other EN-DLBCL; *P*=0.02) (*Online Supplementary Figure S1*). Most of the patients with stage I-bone (68%, n=23) underwent consolidative radiotherapy (Table 3; Figures 2, 3). Advanced stage disease involving the bone had a similar 5y-PFS to nodal disease, and slightly superior to EN-DLBCL (5y-PFS 66% stage IV-bone; 70% stage III and 62% stage IV-EN; *P*=0.01). OS was significantly better in nodal and bone disease compared with EN-DLBCL (5y-OS 80% stage IV-bone; 85% stage III and 71% stage IV-EN; *P*<0.0001). In order to allow for a non-biased comparison between DLBCL-bone and DLBCL-EN, we compared the 300 cases with osseous DLBCL with 600 controls from the EN-DLBCL, matching them based on IPI features (stage, number of EN sites, age, LDH, performance status), and treatment regimen (Figure 4). This case-control analysis showed no statistically significant difference in PFS between bone and other EN sites (*P*=0.1). Slight advantage in OS was still present in osseous cases (*P*=0.02) (*Online Supplementary Figure S1*).

Discussion

This study aimed to evaluate the disease course of DLBCL

Table 2. Advanced stage diffuse large B-cell lymphoma - baseline characteristics.

Total N=1,094	Stage III-nodal N=279	Stage IV-bone N=258	Stage IV-EN N=557	*P* overall	*P* bone *versus* other EN
Age in years, median (IQR)	61.0 (51.0-71.5)	62.0 (46.0-70.0)	65.0 (53.0-74.0)	<0.001	-
Sex F, N (%)	125 (44.8)	105 (40.7)	261 (46.9)	0.258	0.116
PS ECOG ≥2, N (%)	47 (16.8)	82 (31.8)	181 (32.5)	<0.001	0.920
IPI 3-5, N eval.=1,058, N (%)	103 (38.4)	194 (76.1)	342 (63.9)	<0.001	0.001
Cell of origin (Hans alg), N (%) GCB non-GCB (available for 848 pts)	 130 (46.6) 80 (28.7)	 124 (48.1) 87 (33.7)	 245 (44.0) 182 (32.7)	0.298	0.806
Double-hit, N (%) (available for 155 pts)	5 (18.5)	6 (13.6)	10 (11.9)	0.695	-
Bulk ≥10cm, N (%) (available in 991 pts)	36 (13.4)	44 (18.7)	118 (24.2)	0.001	0.027
≥2 EN sites, N (%)	0	166 (64.3)	183 (32.9)	<0.001	<0.001
LDH>ULN, N (%)	166 (63.8)	178 (72.1)	338 (66.0)	0.119	-
Regimen, N (%) R-CHOP R-EPOCH/R-CHOP-R-ICE	 194 (69.5) 85 (30.5)	 133 (51.6) 125 (48.4)	 374 (67.1) 183 (32.8)	<0.001	<0.001
Cycles, N (%) ≥5 3-4 Incomplete/POD/TRM	 263 (94.3) 5 (1.79) 11 (3.94)	 249 (96.5) 2 (0.78) 7 (2.71)	 507 (91.0) 16 (2.87) 34 (6.10)	0.055	0.088
Radiation therapy, N (%)	6 (2.15)	24 (9.30)	40 (7.18)	0.002	0.365
ORR, N (%)	261 (93.5)	245 (94.9)	492 (88.3)	0.004	0.179
CR %	91.0	93.4	85.8	-	-

EN: extranodal; IQR: interquartile range; F: female; PS ECOG: performance status by Eastern Cooperative Oncology Group; IPI: International Prognostic Index; eval.: evaluated; Hans alg: Hands algorithm; GCB: germinal center B-cell derived; pts: patients; LDH: lactate dehydrogenase; ULN: upper limit of normal; R-CHOP: rituximab, cyclophosphamide, adriamycin, vincristine and prednisone; R-EPOCH: rituximab, etoposide, cyclophosphamide, adriamycin, vincristine and prednisone; R-ICE: rituximab ifosfamide, carboplatin, etoposide; POD: progression of disease; TRM: treatment-related mortality; ORR: overall response rate; CR: complete remission.

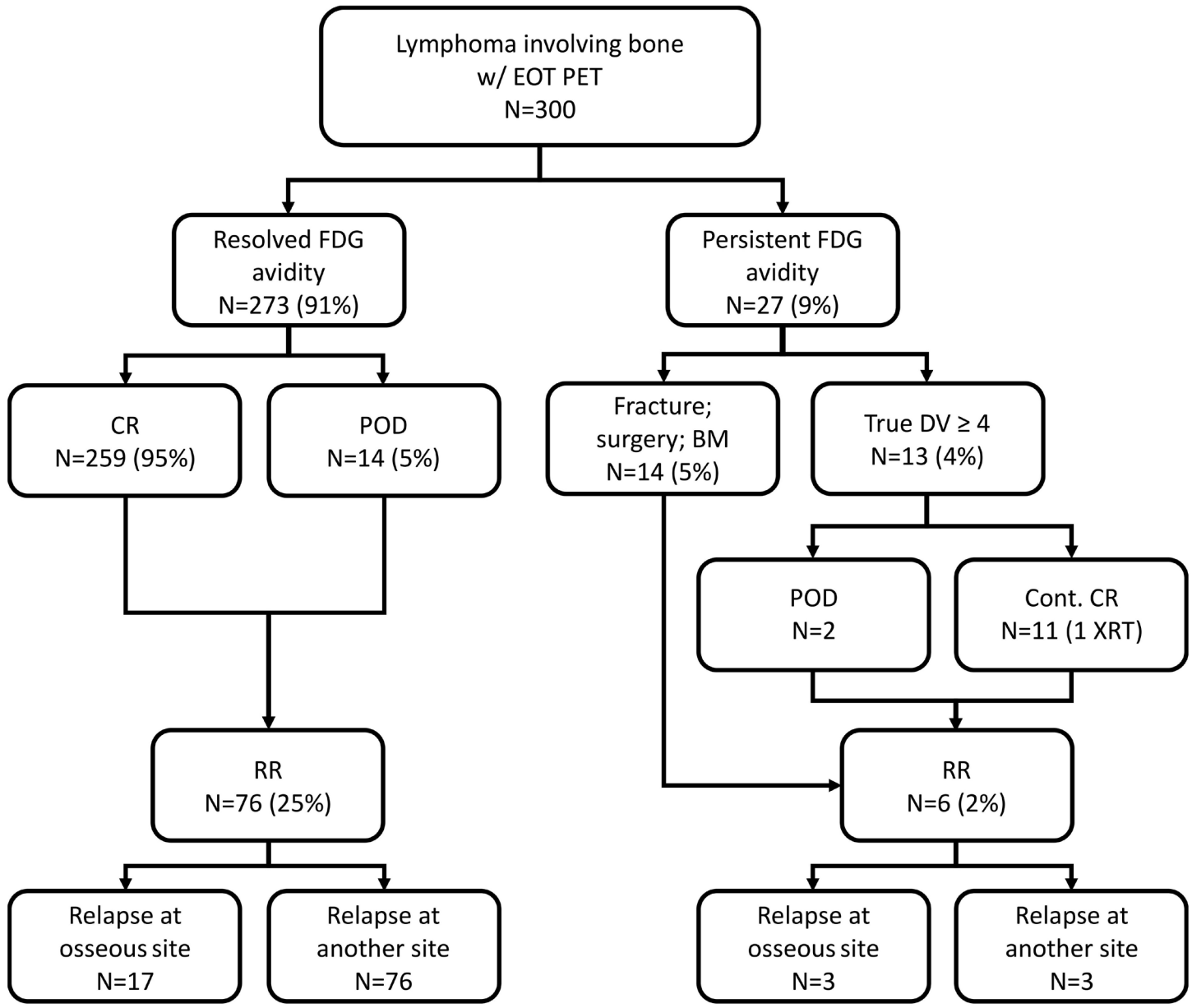

Figure 1. Consort diagram of diffuse large B-cell lymphoma bone cases. Consort diagram of diffuse large B-cell lymphoma bone (DLBCL-bone) cases comparing resolved *versus* persistent fluorodeoxyglucose (FDG) avidity at initial osseous site. Of 16 cases with refractory disease, 14 had a refractory disease but resolution of uptake at the initial osseous site, 2 had a refractory disease with uptake in both osseous and other sites. Of 82 cases with relapsed or refractory (R/R) disease only 20 cases involved the initial osseous sites. w/EOT PET: with end-of-treatment positron emission tomography; CR: complete response: POD: progression of disease: BM: bone marrow involvement; DV: Deauville; Cont.: continuous: XRT: radiation therapy.

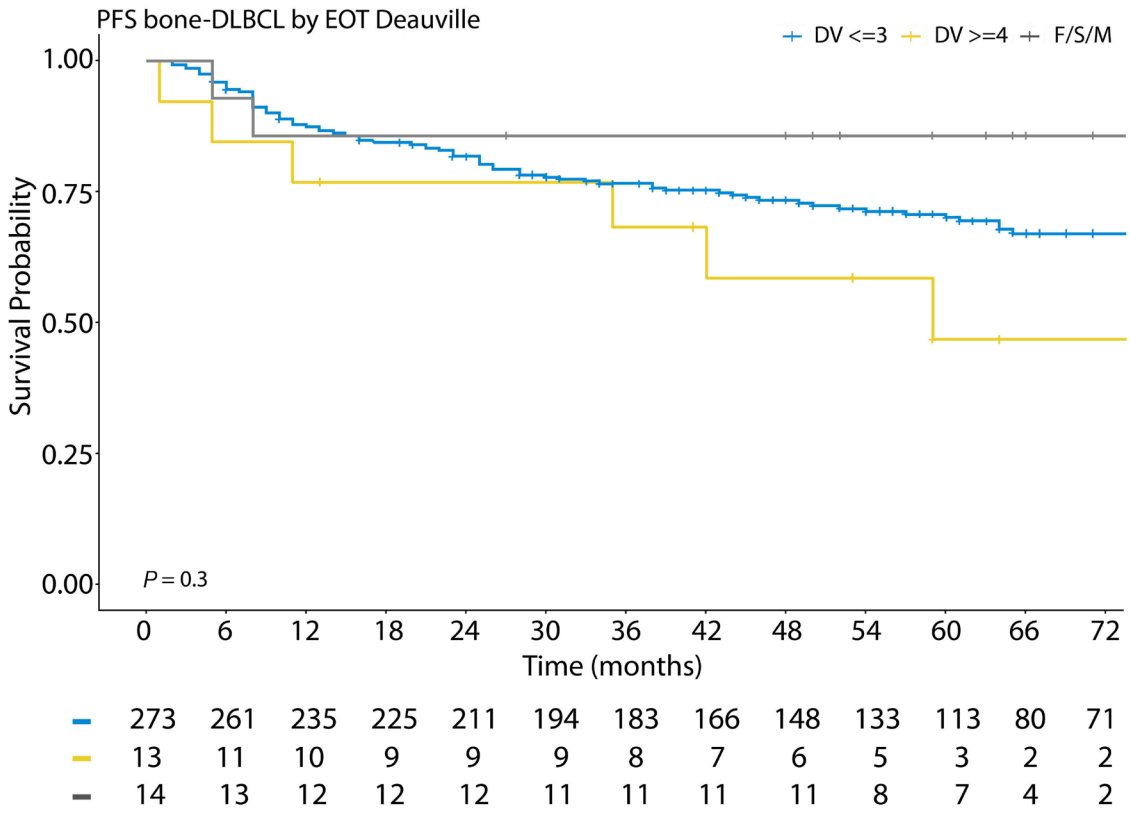

Figure 2. Progression-free survival of diffuse large B-cell lymphoma bone cases by end-of-treatment positron emission tomography response. Comparing patients with Deauville (DV) ≤3, DV ≥4, or with fractures/surgery/marrow (F/S/M) avidity. PFS: progression-free survival; DLBCL-bone: diffuse large B-cell lymphoma bone; EOT end of treatment.

involving osseous site as compared to disease involving other EN and nodal site, with a particular focus on response evaluation by PET/CT. We reviewed data of 1,860 patients with DLBCL treated with RCHOP/RCHOP-like regimens of whom 16% had cortical bones involvement. We demonstrate that osseous involvement in and of itself does not portend a worse prognosis compared to other sites of extra-nodal disease. Further, though residual FDG avidity at osseous sites may be seen in approximately 10% of patients, residual disease seems rare and is usually associated with presence of extra-osseous disease.

The rate of osseous involvement in our cohort is considerably higher than that described in prior studies using CT, but similar to that described with the use of PET for baseline staging.[8,27,28] For example, in a meta-analysis of patients with advanced stage DLBCL treated on nine prospective trials (n=3,840) of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL), the rate of osseous involvement by CT was approximately 8%, as compared to a sub study of CALGB 50303 in which the reported rate of osseous involvement by PET-CT was approximately 20%.[27] In keeping with prior studies, DLBCL-bone, in and of itself, was not associated with a worse prognosis. A similar observation was made in a retrospective study of 60 patients with DLBCL-bone compared with 181 historical controls with EN-DLBCL matched by IPI score and by presence of bone marrow involvement. This study demonstrated no differences in outcome, with a 5-year PFS of 54% and OS 59%.[9] Similarly, in the FLYER study, the outcome of patients with localized disease of the bone was virtually identical

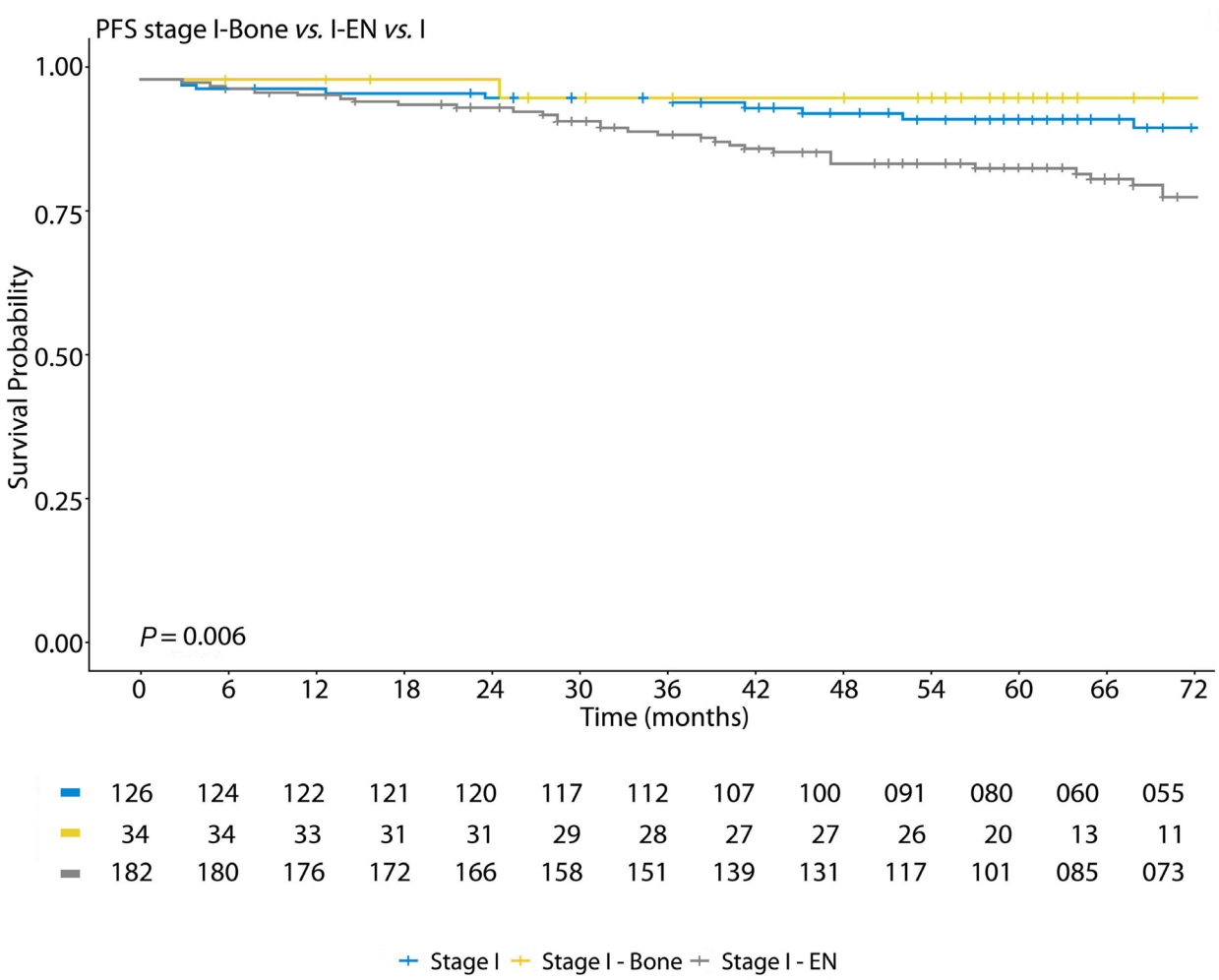

Figure 3. Progression-free survival of limited stage diffuse large B-cell lymphoma. PFS: progression-free survival; EN: extranodal.

Table 3. Overall and progression-free survival by stage.

	Patients N	5y-PFS median (IQR)	HR median (IQR)	*P*	5y-OS median (IQR)	HR median (IQR)	*P*
Limited							
I/II-nodal	453	0.93 (0.9-0.95)	-	1.0	0.87 (0.84-0.9)	-	-
I/II-bone	42	0.95 (0.88-1)	0.71 (0.22-2.27)	0.56	0.92 (0.83-1)	0.48 (0.15-1.53)	0.21
I/II-other EN	271	0.88 (0.84-0.93)	1.55 (1.07-2.24)	0.02	0.84 (0.79-0.89)	1.42 (1.03-1.97)	0.03
Advanced							
III-nodal	279	0.70 (0.65-0.76)	-	-	0.85 (0.81-0.9)	-	-
IV-bone	258	0.66 (0.61-0.73)	1.05 (0.8-1.39)	0.71	0.8 (0.74-0.85)	1.13 (0.8-1.58)	0.49
IV-other EN	557	0.62 (0.58-0.66	1.38 (1.1-1.72)	0.01	0.71 (0.67-0.75)]	1.84 (1.4-2.41)	<0.0001

5y-PFS: 5-year progression-free survival; 5y-OS: 5-year overall survival; HR: hazard ratio; IQR: interquartile range; EN: extranodal.

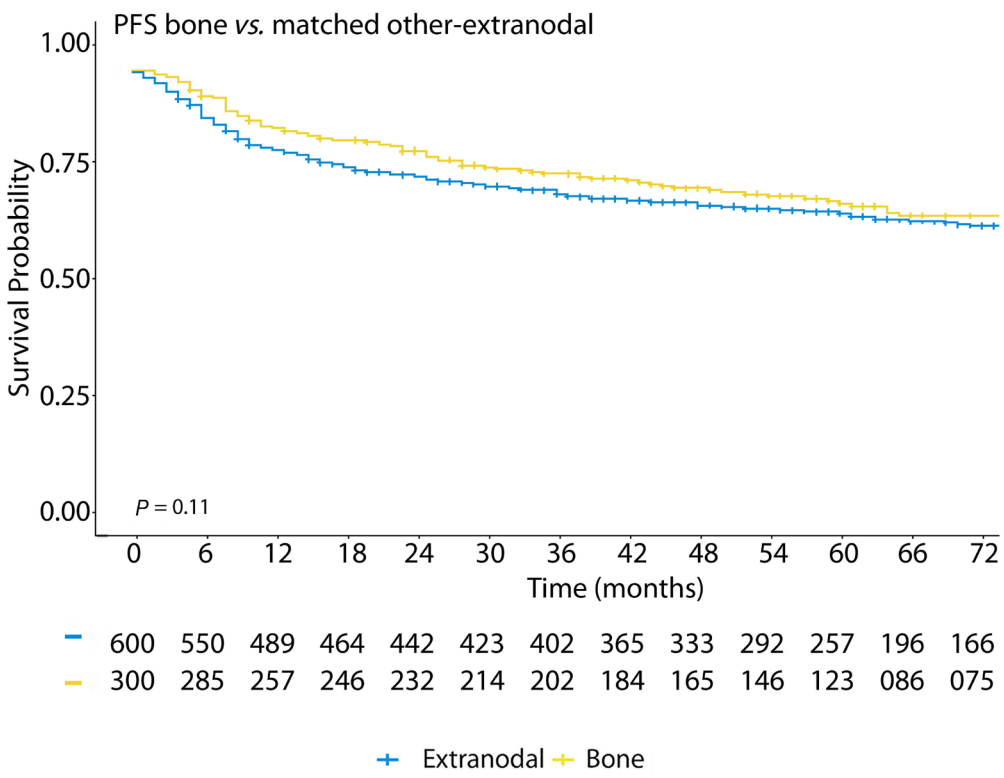

Figure 4. Progression-free survival of matched diffuse large B-cell lymphoma bone and extranodal diffuse large B-cell lymphoma. PFS: progression-free survival.

to those with other localized sites of DLBCL.[28] In contrast, in the meta-analysis by the DSHNHL, skeletal involvement by CT was associated with a worse outcome after RCHOP (hazard ratio event-free survival =1.5) with a benefit from radiotherapy consolidation to bony sites.[8] These differences may be explained, in part, by the limited ability of CT to identify bone involvement (6%, n=60 among patients treated with RCHOP) and absence of data whether in cases considered R/R the site of residual or relapsing the disease was the initial osseous site or another site of disease.

A possible explanation for the widespread notion that DLBCL-bone has a worse outcome is the relatively high rate of FDG uptake at the end of therapy at osseous sites, which in the absence of a confirmatory biopsy, may be falsely regarded as sites of refractory disease. In our study, nearly 10% (n=27) of the patients demonstrated residual bone uptake with intensity greater than liver reference region. However, the positive predictive value (PPV) of this finding was very low. After excluding causes of false-positive FDG uptake (i.e., fracture, surgery, marrow reactivity), the PPV was only 15% (2/13), only two cases were confirmed to truly have residual disease. This PPV is much lower than that reported for residual FDG uptake in nodal sites (ranging from 50% to 100%).[29-32] Concordant with the Lugano criteria, we, therefore, recommend to verify suspicion for residual disease by either a biopsy, alternative imaging method such as magnetic resonance imaging or a repeated PET/CT before proceeding with further treatment.[23]

Importantly, our data demonstrate that physicians at a large academic center treat patients with advanced stage osseous involvement more aggressively than those with EN non-osseous disease. Yet, 91% of DLBCL-bone patients demonstrated a cardiovascular magnetic resonance at osseous sites irrespective of their overall systemic response, and less than a third of all relapses involved the initial osseous sites. These data do in fact suggest an excellent penetration and local control for chemotherapy at osseous sites.[33]

In patients with limited stage disease we confirmed the prior observation of excellent outcomes of standard treatment with no relapses observed in 38 patients with stage IE disease.[11,13,20,34,35] Unlike patients with advanced-stage disease, they were not treated more aggressively than other limited stage patients with nodal or EN disease, though most (68%) received RT consolidation after a short course of R-CHOP.

In conclusion, bone involvement in DLBCL, in and of itself, does not portend a worse prognosis. Residual bone FDG uptake with intensity greater than liver reference (DV ≥4) can be seen in 5-10% of cases. However, unlike nodal disease, this finding is only a weak predictor of refractory disease. In the absence of clear signs of refractory disease at other sites or a confirmatory biopsy showing DLBCL, these sites of residual bone uptake can often be monitored expectantly.

Disclosures

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Contribution:
EJ, PG and SA designed the research. SA developed the script in R and performed the analyses. SA generated the vocabularies. PG assisted with script development. SA and SZ reviewed the notes for gold-standard generation. HS, LM and RN re-reviewed the PET/CT images. EJ supervised note review and resolved questionable cases. EJ, EL and PG wrote the manuscript. All authors reviewed and approved the manuscript.

Data-sharing statement
All the individual participant data collected during the trial are available after de-identification. Data are available upon reasonable request to the corresponding authors.

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