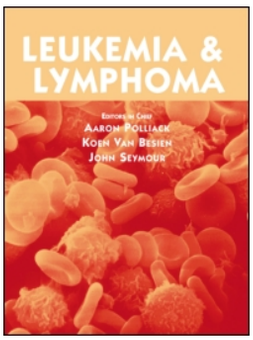

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Primary bone diffuse large B-cell lymphoma: a retrospective evaluation on 76 cases from French institutional and LYSA studies

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ABSTRACT

Primary bone diffuse large B-cell lymphoma (PB-DLBCL) is a rare DLBCL location variant. We treated 76 PB-DLBCL patients by immuno-chemotherapy, resulting in an 84% sustained complete remission rate and a 78.9% survival over a 4.7-year median follow-up period. Ann Arbor stage IV and high age-adjusted international prognostic index were predictive of adverse outcome in univariate analysis. In multivariate analysis using a Cox model, only aa-IPI predicted long-term survival. While based on a limited number of cases, we suggested that radiotherapy may be useful as a consolidation modality in PB-DLBCL. We also suggested that positron emission tomography/CT scan should be interpreted with caution due to a persistent [18F]fluorodeoxyglucose [18FDG] uptake of bone lesions even after remission in some in PB-DLBCL patients. Our study based on a homogeneous cohort of PB-DLBCL patients confirmed the favorable outcome of this DLBCL variant and support the implementation of prospective clinical trials in this disease.

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aa-IPI; DLBCL; radiotherapy; rituximab; primary bone lymphoma

Introduction

Primary bone diffuse large B cell lymphoma (PB-DLBCL) is a rare type of extranodal lymphoma accounting for less than 2% of non-Hodgkin lymphomas [1] and 3% of bone malignancies.[2] This entity includes localized PB-DLBCL characterized by a single bone lesion (stage IE) without or with (stage IIE) regional lymph node involvement, and multifocal PB-DLBCL defined by multiple bone lesions without lymphatic or visceral involvement (stage IV). PB-DLBCL is frequently revealed by pain and/or mass along skeletal structures. Femur (13–33%), pelvis (11–15%), humerus (11–13%), tibia (5–20%) and vertebrae (5–32%) bones are frequently involved. Fractures can occur in 10% to 22% of cases at diagnosis.[3–5] In most reports, a majority of patients have a localized disease while multifocal disease is found in less than 25% of the cases.[6,7] Among bone lymphomas, DLBCL is the most commonly found (78% to 97% of cases) and germinal and non-germinal center histological subtypes are equally represented.[8,9] Other subtypes found in a minority of cases include follicular, lymphoplasmocytic, anaplastic large cell, NK/T cell, Burkitt's lymphoma and Hodgkin lymphoma.[1,6,7,10,11] Currently, the standard of care is systemic chemotherapy – mostly the CHOP regimen combined with rituximab immunotherapy – leading to

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Supplemental data for this article can be accessed here.

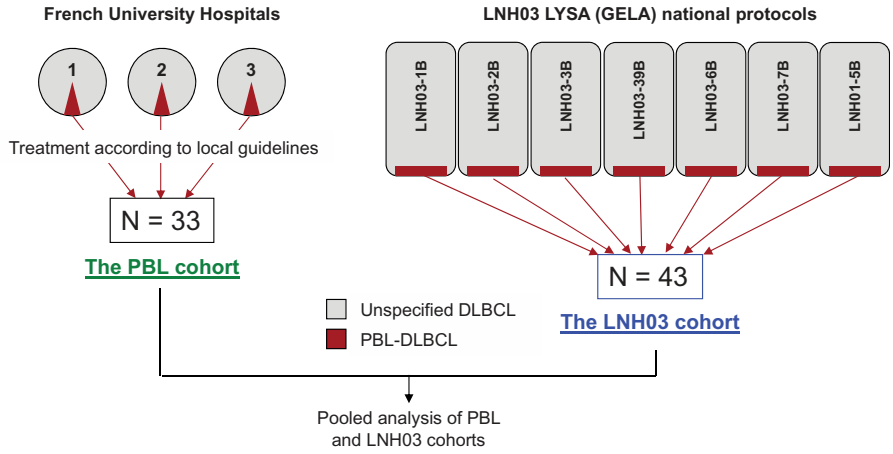

Figure 1. Flow-chart of our study including PBL and LNH03 cohorts.

a cure in a majority of patients.[12,13] Combined radio/chemotherapy strategy appeared promising in some studies but has to be evaluated more widely in PB-DLBCL.[14] In most studies, histological subtypes and clinical entities (i.e. primary versus systemic bone involvement) of lymphoma are mixed. As we believe that DLBCL with pure bone involvement may share common features and similar therapeutic response, we aimed to report here our experience on 76 cases of PB-DLBCL. The objectives of this study were to assess therapeutic response of PBL-DLBCL to immuno-chemotherapy on progression-free and overall survival (PFS and OS, respectively) and to search for clinical, biological or morphological ([18F]fluorodeoxyglucose (18FDG) positron emission tomography/CT scan) markers correlating with to PFS and OS in this cohort.

Methods and patients

We retrospectively collected data from patients treated in three French University Hospital. Inclusion criteria were stage I, II and IV primary bone (PB)-DLBCL. Exclusion criteria were all other nodal and extranodal – including bone marrow – involvement excepted for stage IE and IIE diseases. This cohort was referred to as the PBL cohort. We also addressed this question nationwide through data collected from French LYSA (formerly GELA and thereafter referred to as the LYSA cohort) cooperative group protocols. The LNH03B program of the GELA consisted of 7 prospective multicenter studies of patients with DLBCL older than age 18 years, all of which had a pathology review confirming the DLBCL diagnosis. Patients were stratified on age and age-adjusted International Prognosis Index for treatment allocation in phase II and phase III randomized studies including LNH03-1B,[15] LNH03-2B,[16] LNH03-3B,[17] LNH03-39B,[18] LNH03-6B,[19] LNH03-7B [20] and LNH01-5B [21] (Supplemental Table 1). From these studies, we extracted data on stage I, IE, II, IIE and IV PB-DLBCL patients after LYSA scientific committee approval. Patients from these protocols were referred to as the LNH03 cohort (Figure 1). Hans score was determined retrospectively in 40 (52,6%) tissue samples, 19 in the LNH03 and 21 in the PBL cohort.[22] There was no overlap in patients from PBL and LNH03 cohorts.

Statistical analysis

Qualitative variables (i.e. patients' characteristics and treatment strategies) were described according to the two cohorts (PBL and LNH03 cohorts) but also as a pooled cohort. PFS was measured from the date of randomization to the date of disease progression, relapse, or death from any cause and OS from date of randomization to death from any cause. PFS and OS were analyzed using the log-rank test and expressed as Kaplan–Meier plots. Cox proportional hazards regression model were performed. Univariate analysis was done on PFS and OS to evaluate the prognostic impact of IPI stage, use of rituximab, type of chemotherapy (CHOP versus ACVBP) and post-induction PET evaluation. Multivariate analyses on PFS and OS were performed with a Cox proportional hazards regression model including the variables that were significant in univariate analysis. Differences between the results of comparative tests were considered significant if the two-sided p value was less than .05. Statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

Results

We identified 76 PB-DLBCL patients: 33 in the PBL cohort and 43 in the LNH03 cohort. Specific and

Table 1. Characteristics of PB-DLBCL patients.

	Study dataset		Analyzed set
	LNH2003 $N = 43$	PBL $N = 33$	$N = 76$
Sex			
Male	25 (58.1%)	22 (66.7%)	47 (61.8%)
Female	18 (41.9%)	11 (33.3%)	29 (38.2%)
Age at diagnosis (years)			
Mean (SD)	62.8 (14.56)	47.7 (20.23)	56.3 (18.70)
Median	67.0	47.0	58.5
Min; Max	27; 87	20; 87	20; 87
Chemotherapy			
ACVBP	11 (25.6%)	6 (18.2%)	17 (22.4%)
CHOP	32 (74.4%)	27 (81.8%)	59 (77.6%)
Rituximab			
Yes	43 (100.0%)	33 (100.0%)	76 (100.0%)
Ann Arbor stage			
Stage I	8 (18.6%)	15 (45.5%)	23 (30.3%)
Stage II	3 (7.0%)	6 (18.2%)	9 (11.8%)
Stage IV	32 (74.4%)	12 (36.4%)	44 (57.9%)
Age-adjusted IPI			
0	4 (9.3%)	13 (44.8%)	17 (23.6%)
1	20 (46.5%)	9 (31.0%)	29 (40.3%)
2	14 (32.6%)	5 (17.2%)	19 (26.4%)
3	5 (11.6%)	2 (6.9%)	7 (9.7%)
Missing	0	4	4
Hans score			
GC	15 (78.9%)	11 (52.4%)	26 (65.0%)
Non GC	4 (21.1%)	10 (47.6%)	14 (35.0%)
Missing	24	12	36

pooled characteristics of patients from PBL and LNH03 cohorts are provided in Table 1. There were 47 males and 29 females. Median age at diagnosis was 58. Ann Arbor stage was localized (stage I-II) in 33 (42%) and disseminated (stage IV) in 44 (58%) patients. Forty-six (64%) patients had a low age-adjusted International Prognostic Index (aa-IPI) while aa-IPI was high in 26 (36%) and unavailable for 4 patients. Hans's score available in 40/76 (53%) patients distinguished between germinal center (CG) and non-CG in 26 (65%) and 14 (35%) cases, respectively. All patients received chemotherapy including ACVBP in 17 (22.4%) or CHOP in 59 (77.6%) patients (these chemotherapy regimens are described in Supplemental Table 2). The ACVBP regimen was developed by the French GELA group and compared favorably to CHOP in several clinical trials regardless concurrent use of rituximab.[16,21,23] Incorporation of immunotherapy by the anti-CD20 monoclonal antibody Rituximab into chemotherapy regimens became a standard of care for DLBCL these last 15 years.[24] In fact, all the patients of this study received rituximab combined with CHOP or ACVBP chemotherapy regimens. Radiotherapy was given to 15 (19.7%) patients. For 11 of them, radiotherapy was performed as a planned consolidation therapy after immunochemotherapy according to local guidelines. These patients had mostly stage I–II disease and 10 of them experienced long-term complete remission while one patient underwent salvage chemotherapy and autologous stem cell transplantation (ASCT). Four patients received radiotherapy as a salvage therapy, generally in combination with chemotherapy and two of them successfully received ASCT (Supplemental Table 3). Among our patients, 38 (52.8%) had post-therapy 18FDG positron emission tomography/CT (PET) (PET) evaluation, which was positive in 12 (32.4%) and negative in 25 (67.6%).

Median follow-up was 4.7 years (95% confidence interval (CI) 3.7–5 years; range 0.1–7.7 years). The median OS and median PFS were not reached and 7.1 years, respectively (Figure 2). The 4-year estimated PFS and OS probability were 74.3% (CI: 62.1–83.1%) and 80% (CI: 68.4–87.8%), respectively. Overall, 12 (15.8%) patients had relapsed or progressive disease – which were stage IV diseases for 10 (83%) of them – while 64 (84.2%) experienced sustained complete remission; 16 (21.1%) patients died – 8 from progressive/relapsed disease and 8 from unrelated causes – and 60 (78.9%) are alive. Among relapsed/refractory patients, 11 received salvage therapy involving various chemotherapy regimens and in some cases RT. Three (25%) patients achieved a complete response and successfully underwent ASCT. Two patients achieved a partial response after chemotherapy and one of them had also radiotherapy. The remaining 8 patients (66%) were treated with chemotherapy or RT and had progressive disease (Supplemental Table 4).

In our cohort we searched for correlations between patient characteristics – including Ann Arbor stage, aa-IPI, Hans score, type of treatment (ACVBP and CHOP), use of radiotherapy and post-induction PET results – and outcome. In univariate analysis, we observed a significant difference in PFS with a 4-year estimated PFS of 89.5% (CI: 70.7–96.5%) versus 63.4% (CI: 46.1–76.4%) and OS of 93% (CI: 74.7–98.2%) versus 70.7% (CI: 53.7–82.4%) for Ann Arbor stage I–II versus IV, respectively. Among our cohort of patients, two (6.3%) deaths occurred in stage I–II and 14 (31.8%) in stage IV disease ($p = 0.011$, Supplemental Figure 1). We also investigated the impact of aa-IPI, with an estimated 4-year PFS probability of 87.8% (CI: 73–94.8%) versus 47.4% (CI: 26.5–65.7%) and 4-year OS probability of 94.8% (CI: 80.8–98.7%) versus 51.3% (CI: 29.9–69.2%) in aa-IPI 0–1 and 2–3, respectively. Three (6.5%) death occurred in 0–1 aa-IPI patients and 13 (50%) in 2–3 aa-IPI patients ($p < 0.0001$, Figure 3). Also, age over 60-year-old adversely influenced prognosis as shown in Supplemental Figure 2. Conversely, Hans's score, radiotherapy and PET results had no prognosis impact in our cohort (data not shown). Concerning the type of immunochemotherapy, while no statistically significant difference was found, a trend to a better survival was observed in patients treated with RACVBP compared to

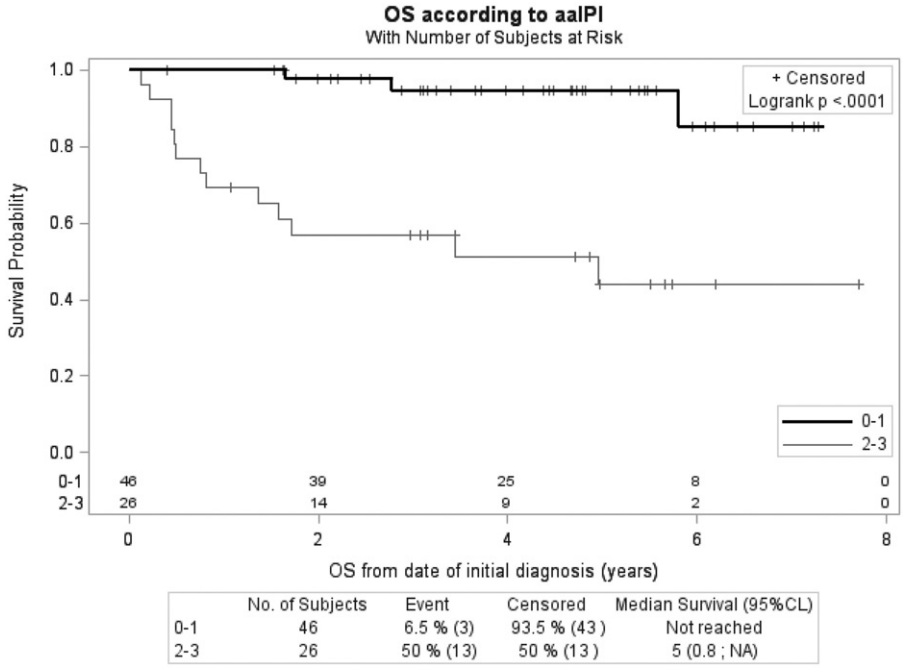

Figure 2. Survival of the 76 PB-DLBCL patients. (A) Progression-free survival (PFS) and (B) overall survival (OS) curves. The number of patients at risk is indicated at each time marker. Time-scale is in years.

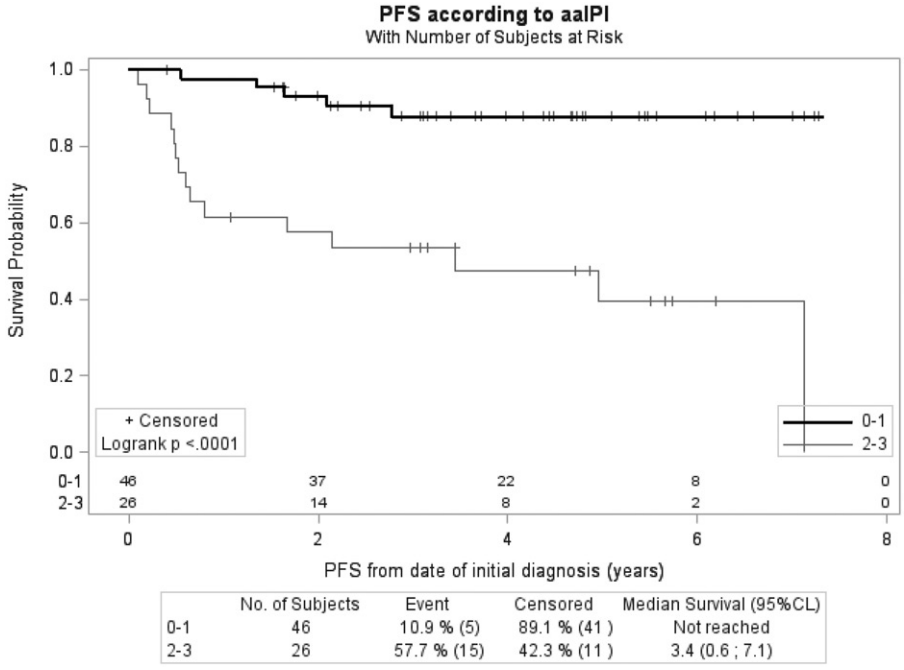

Figure 3. Survival according to aa-IPI. (A) PFS and (B) OS curves. Patients were separated based on aa-IPI score. 0–1 black line and 2–3 grey line. Comparison between survival curves is given by a log-rank test.

RCHOP (Supplemental Figure 3). In multivariate analysis, aa-IPI was the only variable demonstrating a significant impact on survival using a Cox model. Indeed, high aa-IPI score adversely impacted on PFS (hazard ratio: 11.315; CI: 1.817–70.477; $p = 0.0093$) and OS (hazard ratio 19.752; CI: 1.721–226.686; $p = 0.0166$).

Discussion

PB-DLBCL is a rare variant accounting for 1.4% to 3.8% of DLBCL included in our various LNH03 trials (Supplemental Table 5). While mentioned in the 2008 WHO classification,[25] PB-DLBCL is not recognized as a unique entity in contrast to other location variants

Table 2. Summary of PB-DLBCL studies.

1st author	*N*	A	Stage	Histo	Treatment	OS	Ref.
Rathmell	27	58	IE: 85% IIE: 15%	ND	C + RT: 33% RT: 56% SC: 11%	RT 40% C + RT 88%	[13]
Dubey	45	ND	IE: 67% IIE: 33%	DLBCL: 91%	C + RT: 80% RT: 11% C: 9%	5 years: 68%	[1]
Zinzani	52	58	IE/IIE: 100%	DLBCL: 85%	C + RT: 63% C: 15% RT: 21%	9 years: 68% Relapse: C + RT: 3.5% C: 14% RT: 57%	[11]
Barbieri	77	42	IE: 56% IIE: 44%	DLBCL: 97%	C + RT: 87% RT: 13%	15 years: 88.3%	[32]
Beal	82	48	IE: 78% IIE: 4% IV: 19%	DLBCL: 85%	C + RT: 57% RT: 14% C: 30%	5 years: 88% C or RT: 78% C + RT: 96%	[7]
Ramadan	131	63	IE: 26% IIE: 20% IV: 71%	DLBCL: 79%	C: 44% C + RT: 48% SC: 12%	5 years: 62% 10 years: 41%	[5]
Heyning	36	48	IE/IIE: 100%	DLBCL: 100% GC: 53% ABC: 22% Other: 25%	C + RT: 69% RT: 14% C: 11% Other: 6%	5 years: 75%	[9]
Alencar	53	52	IE 66% IIE: 11% IVE: 23%	DLBCL: 83%	C + RT: 62% RT: 12% C: 21%	3 years: 100%	[6]
Cai	116	50	IE: 80% IIE: 20%	DLBCL: 78%	C + RT: 75% RT: 13% C: 12%	5 years: 76%	[10]
Wu	70	56	IE: 27% IIE: 29% IV: 44%	DLBCL: 74%	C: 47% C + RT: 47% Other:6%	5 years: 81% 10 years: 75%	[33]
Messina	37	53	IV: 100%	DLBCL: 100%	C + RT: 65% C: 35%	5 years: 74%	[27]
Bruno-Ventre	161	55	I: 87%	DLBCL: 100%	C + RT: 78%	5 years: 75%	[34]
Tao	102	55	I-II: 70%	DLBCL: 100%	C + RT: 66% Rituximab: 72%	5 years: 82%	[14]
Pilorge	76	56	I-II: 42% IV: 58%	DLBCL: 100%	Riyuximab: 100% RT: 20%	6 years: 71%	

N: number of patients; A: median age; Stage: stage according to Ann Arbor classification; Histo: histological informations; OS: overall survival; Ref: reference; ND: not done; C: chemotherapy; RT: radiation therapy; SC: supportive care.

such as primary mediastinal, central nervous system and "leg-type" cutaneous DLBCL.[26] Indeed, PB-DLBCL does no share unique phenotypic or gene expression profiling features or specific response to therapy and is therefore not considered separately in clinical trials.

Several retrospective studies reported PB lymphomas separately and suggested that these topographic variants may have a seemingly favorable prognostic particularly when combining chemotherapy and radiation therapy (Table 2).[7,11,13,27] However, these studies report heterogeneous data and while DLBCL is the most frequently described histological subtype, other lymphomas are reported including follicular or anaplastic types. In contrast to most studies (Table 2), we excluded from our analysis non-DLBCL lymphomas. Moreover, therapeutic option used may also markedly differ among individual cohorts. In our current study, we focused on DLBCL with pure bone involvement treated homogeneously with either CHOP or ACVBP regimens in combination with rituximab in all cases.

As PB-DLBCL is a very rare entity, we collected cases across three University Hospitals particularly involved in bone diseases (the PBL cohort) and also nationwide through the LNH03 database from the LYSA study group including seven prospective clinical trials on DLBCL (the LNH03 cohort). The patients from these two cohorts displayed similar clinical characteristics except concerning stage I diseases, which were generally excluded from LNH03 studies except for LNH03-7B and LNH03-1B studies (74.4% versus 36.4% stage IV diseases in the LNH03 and PBL cohorts, respectively, Table 1). In fact, this difference may explains the better outcome observed in the PBL cohort compared to the LYSA cohort (PFS 84.8% versus 65.1% and OS 90.9% versus 69.8%, respectively, Supplemental Figure 4) and was not apparent after multivariate analysis. Similar to other studies, we found that PB-DLBCL had a favorable outcome as 78.9% of the patients were alive and in complete remission with a median follow-up of almost five years. These results are superior to those observed

in DLBCL clinical trials generally ranging from 60% to 70% OS [1,5,10,11] and are in agreement with studies specifically focusing on PB-DLBCL with survival probabilities ranging from 68% to 100% (Table 2). In univariate analysis, we found that age over 60, advanced Ann Arbor stage and high aa-IPI adversely impacted on prognosis. After multivariate analysis, the only predictive marker for PFS and OS among our cohort was aa-IPI.

In DLBCL, PET performed at the end of treatment has shown a high predictive value for PFS and OS.[28] Post-treatment persistent 18FDG uptake was found in 32% of evaluable patients, which was higher than expected compared to up to 20% of PET positivity in most DLBCL studies.[28] We did not detect a prognostic impact of post-treatment PET positivity in our current study. However, only 50% of patients had a metabolic response assessment which limited the robustness of our conclusions concerning PET evaluation in PB-DLBCL. In a limited number of patients ($n = 8$) from the PBL cohort, we found that in long-term follow-up (between 6 and 24 months after treatment completion), PET was negative or with SUV below the background noise, while magnetic resonance imaging (MRI) was still abnormal (data not shown). These particularities might be due to the particular course of bone healing. These results require further validation in larger/prospective cohorts but suggest that outside of clinical trials, PET scan positivity should not be used as a decision marker for salvage therapy regardless the overall context, as suggested by other reports.[29]

The role of radiation therapy (RT) remains a matter of debate in DLBCL as a consolidation modality after chemotherapy [5,14,30] In our study, post-induction RT was given to 11 (33%) patients from the PBL cohort but was not part of any LNH03 protocol, preventing any relevant comparison of survival data regarding RT. However, 10 of the 11 patients of the PBL cohort – mostly localized diseases – treated with radiotherapy as a consolidation strategy after immunochemotherapy experienced long-term complete remission, suggesting a potential favorable impact of this strategy. This hypothesis is supported by recent data by Tao and colleagues, suggesting that RT may be useful as a consolidation modality after conventional immunochemotherapy in PB-DLBCL.[14] In a large study on DLBCL with skeletal involvement (which included 52 cases of PB-DLBCL), Held and coworkers also demonstrated a positive impact of radiotherapy on survival.[31] The question of RT as a therapeutic modality in PB-DLBCL – in combination with immunochemotherapy – may represents a pivotal question for future prospective clinical trials.

In our current study, we show that PB-DLBCL demonstrate a good prognosis when treated by immuno-chemotherapy. In addition, we suggest that radiotherapy may be useful in PB-DLBCL and that PET analysis should be used with caution as persistent 18FDG uptake may not necessarily implies treatment failure. Building on previous reports highlighting the specificities of PB-DLBCL particularly in terms of favorable outcome, our current study emphasizes the need for PB-DLBCL prospective clinical trials in the future.

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