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Utility of the Central Nervous System International Prognostic Index in patients with primary mediastinal large B-cell lymphoma treated with rituximab-containing chemoimmunotherapy

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Running Head: Utility of CNS-IPI in PMBCL

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Data Sharing Statement: The original data are available upon request by contacting the corresponding author.

Authorship Contributions

K.J.S. and J.Y. conceived and designed the study; AJ performed statistical analysis; D.V., A.S.G., C.P.V., D.W.S., A.R.H., L.H.S. data collection and analysis; PF pathology review; J.Y. and K.J.S. wrote the manuscript; all authors edited and approved the final version of the manuscript.

Conflict of Interest Disclosures

J.Y. reports honoraria from BeiGene/BeOne and Sanofi. D.V. reports honoraria and advisory boards from AbbVie, Janssen, Kite/Gilead, AstraZeneca, Roche, BeiGene, Bristol Myers Squibb/Celgene, Merck, and Zetagen and research funding (to the institution) from AstraZeneca and Roche. A.S.G. reports honoraria from AbbVie, AstraZeneca, Janssen, and Beigene/BeOne and research funding (to the institution) from AbbVie, AstraZeneca, Janssen, Roche, and Loxo Oncology. C.P.V reports honoraria from Jansen, AbbVie, Pfizer, Sanofi, Forus, and Amgen. D.W.S. reports consultancy for AbbVie, AstraZeneca, Chugai, GenMab, Incyte, Roche, and Veracyte; research funds from Janssen and Roche/Genentech; and named inventor on a patent describing the use of gene expression to subtype aggressive B-cell lymphomas, one of which is licensed to nanoString Technologies. L.H.S. reports consulting and honoraria from AbbVie, Acerta, Amgen, Apobiologix, AstraZeneca, Celgene, Chugai, Gilead, Incyte, Janssen, Kite, Karyopharm, Lundbeck, Merck, Morphosys, Roche/Genentech, Sandoz, Seattle Genetics, Servier, Takeda, Teva, TG Therapeutics, and Verastem and research funding from Roche/Genentech and Teva. K.J.S. reports honoraria/consultancy from SeaGen and Roche; research funding from Bristol Myers Squibb; institutional research funding Roche, Merck, Seagen, Viracta, and AstraZeneca; Data Safety Monitoring Committee (DSMC) for Regeneron; and Steering Committee for Corvus. The remaining authors declare no competing financial interests.

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Primary mediastinal large B-cell lymphoma (PMBCL) was recognized as a distinct entity over 15 years ago based on distinct clinico-pathological features, including the mandatory presence of a predominant anterior mediastinal mass. Although typically confined to the intrathoracic region, extrathoracic disease can occur, including rare renal/adrenal involvement, and is associated with an inferior prognosis.[1, 2] Despite overall favourable outcomes with frontline therapy, central nervous system (CNS) relapse has been reported in approximately 2.5-4.5% of patients treated with non-rituximab-containing regimens.[2] There are limited studies evaluating CNS relapse risk and associated risk factors in the rituximab era. The CNS-international prognostic index (CNS-IPI) is a CNS risk model, developed and validated in diffuse large B-cell lymphoma (DLBCL) treated with rituximab-containing anthracycline-based chemotherapy, which incorporates the standard IPI risk factors in addition to renal/adrenal involvement.[3] As a composite score, the CNS-IPI can identify a high-risk group with ≥4 risk factors, with a CNS relapse risk of ≥10%; however, as a separate entity, PMBCL was not included in this study. Here, we evaluate the utility of the CNS-IPI in patients with PMBCL treated with frontline rituximab-based therapy.

Patients age ≥17 years with newly diagnosed, treatment naïve PMBCL, who received curative intent rituximab-containing chemoimmunotherapy between January 1, 2001 and December 31, 2022, were identified in the BC Cancer Lymphoid Cancer Database. From 2001-2005, R-CHOP for 6-8 cycles was the recommended standard therapy with planned consolidative radiotherapy. A PET-adapted approach to guide use of consolidative radiotherapy was introduced in 2005, as previously described.[4] In more recent years, DA-EPOCHR has been favoured to mitigate the need for radiotherapy altogether. Central nervous system (CNS) prophylaxis has not been standard in PMBCL and thus, use was at the discretion of the treating physician.

All diagnostic biopsies were reviewed by an expert BC Cancer hematopathologist with additional clinical assessment to confirm the presence of a predominant anterior mediastinal mass in keeping with current diagnostic criteria. The CNS-IPI was determined, incorporating the standard IPI factors of age >60, Ann Arbor stage III/IV, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, number of extranodal sites >1, elevated lactate dehydrogenase (LDH) and renal/adrenal involvement, to stratify patients into low risk (0-1 factors), intermediate risk (2-3 factors), and high risk (≥4 factors) groups.[3] The cumulative incidence of CNS relapse (or systemic only relapse) was estimated using a competing risk analysis (R package cmprsk), accounting for death from any cause as a competing event. This research was approved by the University of British Columbia/BC Cancer Research Ethics Board.

A total of 247 patients were identified. Median age at diagnosis was 36 years and 138 (55.9%) were female (Table 1). The median size of the anterior mediastinal mass was 11 cm (range 5-20 cm). By the CNS-IPI (all factors available in 236 patients), patients were classified as: low risk (0-1 factors) in 96 (40.7%), intermediate risk (2-3 factors) in 102 (43.2%), and high risk (≥4 factors) in 38 (16.1%). In total, 213 patients were planned for R-CHOP and 34 for DA-EPOCHR. Of the patients treated with R-CHOP, 199 received 6 cycles and 12 patients received 7 or 8 cycles as per

physician discretion in the pre-PET era. The remaining 14 patients received less than 6 cycles due to: enrollment in a clinical trial evaluating R-CHOP x 4/R-ICE x 4 (n=8) (one of which received only 1 cycle of R-ICE due to poor tolerance); limited stage disease (R-CHOP x 4, n=1); revised diagnosis from classic Hodgkin lymphoma to PMBCL (ABVD x 2/R-CHOP x 4) (n=1); progressive disease (PD) on R-CHOP n=3; 1 patient each died of toxicity or refused further therapy following cycle 1 (overall median of 6 cycles of R-CHOP). Of the 34 patients who received DA-EPOCHR, 23 received 6 cycles and the remaining 11 patients received 1 cycle of R-CHOP followed by 5 (n=11) or 6 (n=2) cycles of DA-EPOCHR (overall median 6 cycles DA-EPOCHR). Only three patients, all treated with R-CHOP, received CNS prophylaxis with high-dose methotrexate (HD-MTX), all with renal/adrenal involvement (Table 1). Intrathecal chemotherapy was not routinely administered with DA-EPOCHR.

Using reverse censoring, the median follow-up was 8.7 years (range 0.4-21.9). For all patients, the the 5-year progression-free and overall survival were 80% and 91%, respectively. The 5-year cumulative incidence of CNS relapse was 2.7% (95% confidence interval [CI] 1.1%, 5.6%); 5 year cumulative incidence of systemic only lymphoma relapse was 16.3% (95% CI, 11.5%, 21.2%). Clinical and treatment details of the patients who developed CNS relapse are shown in Tables S1/S2. By the CNS-IPI, the 5-year cumulative incidence of CNS relapse was 0%, 1.6% (95% CI 0.1%, 7.7%), and 13.2% (95% CI 4.7%, 26.0%) in the low, intermediate, and high CNS risk groups, respectively (P<0.0001) (Figure 1). Overall, 5.3% (n=13) of all PMBCL patients had renal/adrenal involvement, with a 5-year cumulative incidence of CNS relapse of 30.8% (95% CI 8.7%, 56.6%), in comparison to 1.1% (95% CI 0.2%, 3.8%) in those without involvement (P<0.00001) (Figure 2). Notably, four of six patients with CNS relapse had renal/adrenal involvement at diagnosis (Table S1). For the remaining CNS-IPI factors, only age (P=0.033) and stage 3/4 (P=0.026) reached statistical significance (Table S3). By treatment group, the 5-year cumulative incidence of CNS relapse in those treated with DA-EPOCHR compared to R-CHOP (including R-CHOP/R-ICE) was 6.4% (95% CI 1.1%, 18.9%) vs. 2.1% (95% CI 0.7%, 4.9% (p=0.082) (Figure S1). There were numerically more patients in the DA-EPOCHR group with a high-risk CNS-IPI (20.6%) compared to R-CHOP (15.3%), but the difference was not statistically significant (p=0.442) and the proportion of patients with renal/adrenal involvement in the treatment groups was similar (5.9% [DA-EPOCHR] vs. 5.2% [R-CHOP], p=0.862).

In total, six patients (2.6%) had CNS relapse. Four patients had isolated parenchymal involvement at relapse, one of whom developed systemic relapse later during CNS treatment; one patient had both parenchymal and leptomeningeal involvement; the remaining patient had leptomeningeal disease concurrent with systemic relapse (Table S3). Four patients were treated with curative intent: two received a thiotepa-based autologous stem cell transplant; one patient each received whole brain radiotherapy or pembrolizumab, and all have had durable complete remissions.

Very few studies have evaluated the CNS relapse risk in PMBCL in rituximab-treated patients. Reports are limited by disease and CNS event rarity. Collectively, the CNS relapse risk appears

very similar to reports in the pre-rituximab era, likely reflecting the predominately parenchymal location and poor CNS penetration of rituximab.[5] The LYSA group reported a similar overall CNS relapse rate of 2.9% (9/331) in PMBCL patients treated with rituximab containing regimens across 25 centers, however, risk factors, including the CNS-IPI were not detailed.[6] A multi-center study of 564 adult patients with PMBCL, including 351 patients from the Hellenic database combined with 103 patients from Israeli, Turkish, and Saudi Arabian centers, reported a 2-year cumulative incidence of CNS relapse of only 1.4%, with eight of 564 patients having a CNS event, all isolated and solely parenchymal. Systemic progression was considered a competing event in this study, which may have underestimated the overall risk.[7] In this study, CNS relapse risk was similar in DA-EPOCHR and R-CHOP treated patients. In keeping with our findings, patients with a high-risk CNS-IPI had a higher 2-year cumulative incidence of CNS relapse of 10.4%, compared to only 0.8% in both the low and intermediate risk groups ($p<0.001$). The association with renal/adrenal involvement was also striking, with a 2-year cumulative incidence of CNS relapse of 14.3% (vs. 0% in those without renal/adrenal involvement, $p<0.014$).[7] A study from the Mayo Clinic reported a 2- and 5-year CNS relapse risk of 2.2% in 154 patients with PMBCL treated with either R-CHOP (50%) or DA-EPOCHR (50%), with only 3.3% having received HD-MTX.[8] In contrast to our study and the multi-center report, all three relapsed patients had concurrent CNS and systemic relapse. Only 2% of patients in the Mayo Clinic study had a high risk CNS-IPI, and thus the utility could not be evaluated. Although renal/adrenal involvement was not detailed for all patients, one of three patients with CNS relapse did have adrenal involvement at diagnosis.[8]

Recent studies have highlighted the unique genetic features of PMBCL with an immune evasion phenotype and abundant PDL expression.[9] This has led to studies evaluating PD-1 inhibitors in the relapsed/refractory (R/R) setting. KEYNOTE-013 (phase 1b) and KEYNOTE-170 (phase 2) demonstrated overall response rates (ORR) of 48% and 45% respectively; with a median follow-up time of 29.1 months, the median duration of response had not been reached in either study.[10] Checkpoint inhibitors, including PD-1/PD-L1 antibodies, are known to penetrate the CNS, and are integrated into the treatment of metastatic melanoma, including those with CNS involvement. Notably, one patient in our cohort remains in ongoing durable complete remission following treatment with a PD-1 inhibitor, without any subsequent therapy. CheckMate 647 (NCT02857426) evaluated nivolumab in R/R primary CNS lymphoma and noted a low ORR (10.6%), although steroid use limited the interpretation. Other retrospective studies have demonstrated benefit of PD1 inhibitiors in some patients with R/R primary CNS lymphoma with one analysis including consecutive patients from four centers, demonstrating an ORR of 41% with nivolumab and median duration of remission of 20.9 months.[11] The efficacy may be higher in PMBCL with secondary CNS involvement given the unique biology. Importantly, a phase 3 study incorporating nivolumab with either R-CHOP or DA-EPOCHR (NCT04759586) in newly diagnosed PMBCL is ongoing and may provide further insight into the protective effect against CNS relapse. Regardless, adjusting for the CNS-IPI will be important.

Given the 20 year time frame, management of CNS recurrence was heterogenous in our study. More recent recommendations have endorsed including consolidative thiotepa-based autologous stem cell transplant in the management of secondary CNS lymphoma in DLBCL,[12] which would also be considered in PMBCL. In addition, a meta-analysis assessing the use of

chimeric antigen receptor T-cell therapy for CNS relapse of aggressive B-cell lymphoma, including two patients with PMBCL, showed that almost 50% of patients were in an ongoing remission.[13] Regardless, all patients in our study who received active therapy for CNS relapse remain in complete remission, which is in contrast to earlier studies in R/R PMBCL, which showed an overall dismal prognosis even with systemic only relapse.[14] This highlights the advances of modern therapy which have likely improved outcome in R/R PMBCL, including those with CNS involvement.

Taken together, we highlight the predominant parenchymal location, the utility of the CNS-IPI, and the importance of renal/adrenal involvement in estimating CNS risk in PMBCL. The role of CNS prophylaxis has not been proven in DLBCL and also has an unclear role in high risk PMBCL.[15] Further studies are needed in PMBCL investigating the mechanism of CNS seeding and impact of prophylaxis strategies. With this study as a benchmark, we eagerly await results from front-line studies integrating CNS penetrating agents like PD-1 inhibitors, and their impact on CNS risk.

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Total number of patients	247
Male (%)	109 (44.1)
Female (%)	138 (55.9)
Median age in years (range)	36 (17-84)
Median size of anterior mediastinal mass in cm (range)	11 (5-20)
CNS-IPI risk factors	
Age >60 (%)	21 (8.5)
Stage III/IV (%)	97 (39.3)
Elevated LDH (n=242) (%)	178 (73.6)
Extranodal sites >1 (%)	84 (34.0)
Performance status ≥2 (n=240) (%)	88 (36.7)
Renal/adrenal involvement (%)	13 (5.3)
CNS-IPI risk groups*	
Low risk (0-1) (%)	96 (40.7)
Intermediate risk (2-3) (%)	102 (43.2)
High risk (≥4) (%)	38 (16.1)
Rituximab-chemotherapy	
R-CHOP (like) (%) **R-CHOP (%)** **R-CHOP/R-ICE (clinical trial) (%)**	213 (86.2) 205 (83.0) 8 (3.2)
DA-EPOCHR (%)	34 (13.8)
Consolidative radiation therapy (%)	75 (30.4)
R-CHOP (n=213) (%)	74 (34.7)
DA-EPOCHR (n=34) (%)	1 (2.9)
CNS prophylaxis (%)	3 (1.2)
HD-MTX (%)	2 (67)
HD-MTX + intrathecal therapy (%)	1 (33)

*n=11 missing

Table 1. Baseline characteristics of patients with primary mediastinal large B-cell lymphoma

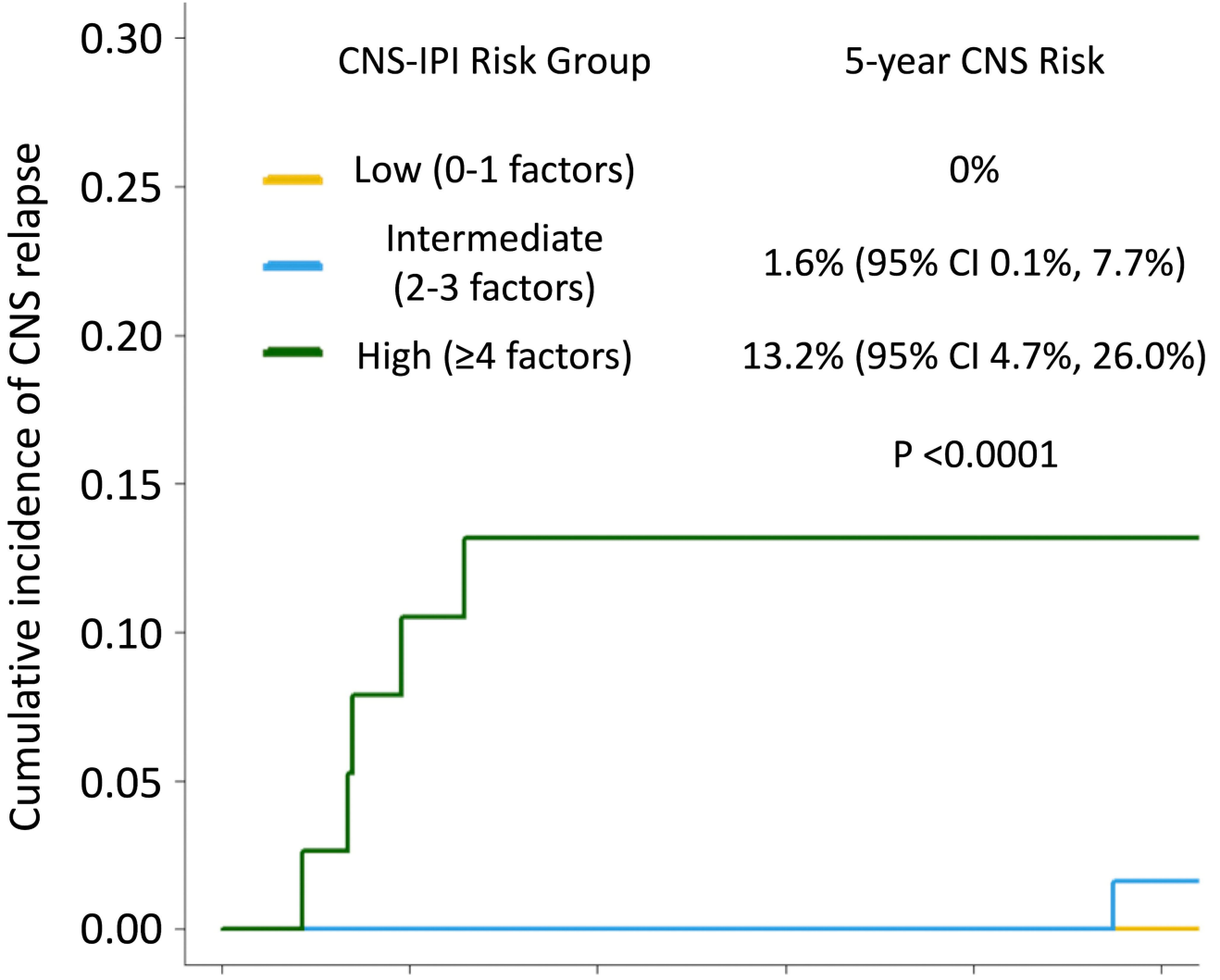
CNS: central nervous system; IPI: International Prognostic Index; LDH: lactate dehydrogenase; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; DA-EPOCHR: dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; HD-MTX: high-dose methotrexate

Figure Legends

Figure 1. Cumulative incidence of CNS relapse, estimated using a competing risk approach with death from any cause as a competing event, stratified by CNS-IPI risk groups. CNS: central nervous system; IPI: International Prognostic Index; CI: confidence interval

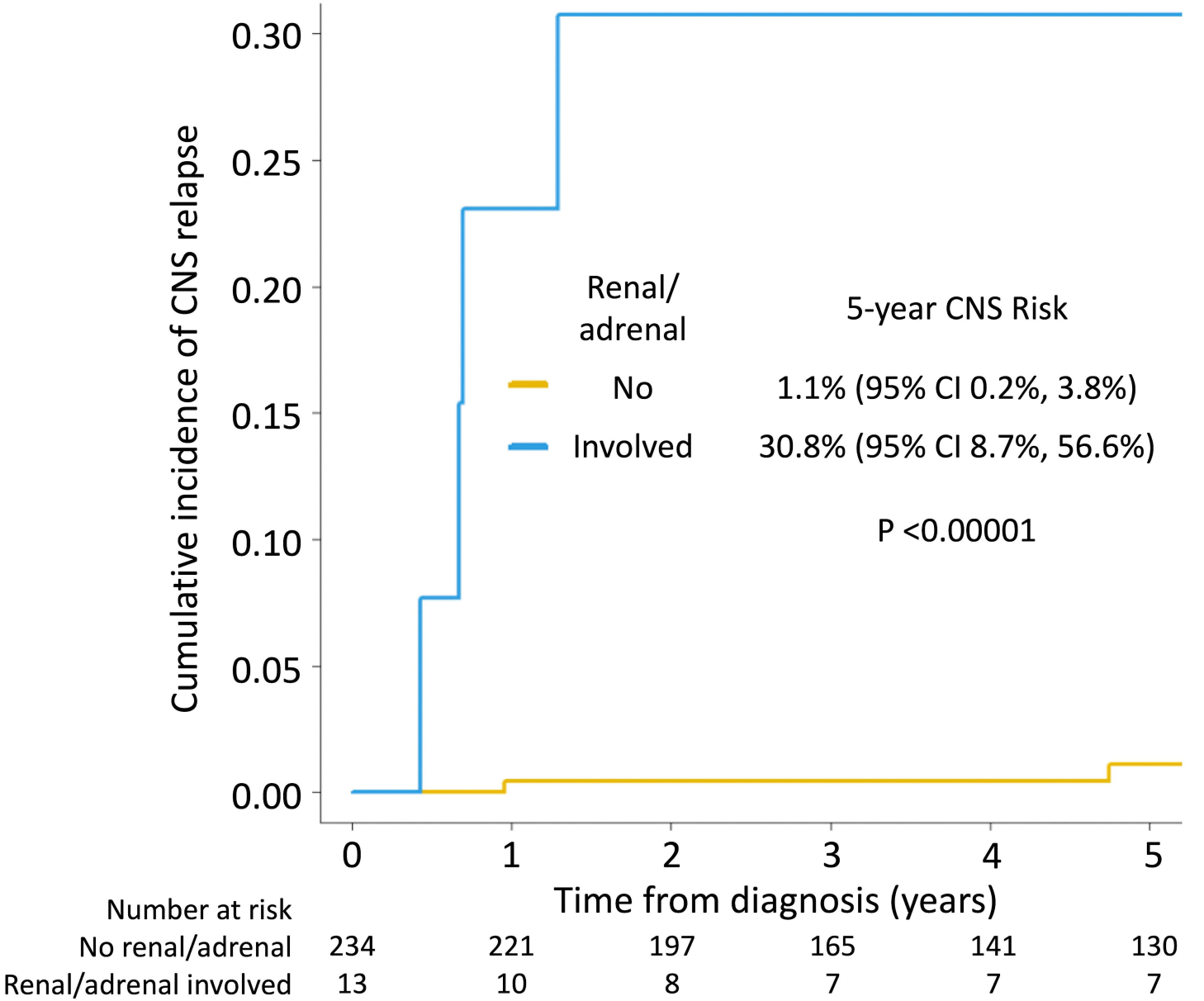
Figure 2. Cumulative incidence of CNS relapse, estimated using a competing risk approach with death from any cause as a competing event, stratified by renal/adrenal involvement. CNS: central nervous system; IPI: International Prognostic Index; CI: confidence interval

Figure 1



Number at risk						
Low risk	96	90	82	72	60	55
Intermediate risk	102	99	85	68	58	52
High risk	38	32	29	24	22	22

Figure 2


Cumulative incidence of CNS relapse
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Renal/ adrenal
No
Involved
5-year CNS Risk
1.1% (95% CI 0.2%, 3.8%)
30.8% (95% CI 8.7%, 56.6%)
P <0.00001
0
1
2
3
4
5
Time from diagnosis (years)
Number at risk
No renal/adrenal 234 221 197 165 141 130
Renal/adrenal involved 13 10 8 7 7 7

Patient	Age	Stage	Anterior mediastinal mass size (cm)	Extranodal Sites	PS	LDH (upper limit of normal)	CNS-IPI Risk	Primary therapy	Response at end of treatment
1	67	IIB	5	None	4	281 (210)	Intermediate	R-CHOP	CR
2	20	IVB	13	Adrenal, kidney, soft tissue, lung, pericardium, pancreas	1	586 (230)	High	R-CHOP	CR
3	84	IVA	10	Pleura, lung, pericardium	2	245 (240)	High	R-CHOP	CR
4	21	IVA	16	Adrenal, kidney, lung, bowels	1	539 (220)	High	R-CHOP	PD (CNS→ systemic)
5	36	IVA	10	Adrenal	2	713 (240)	High	DA-EPOCHR + HD-MTX + IT MTX	PR → RT → PD (CNS)
6	28	IVA	12	Adrenal, stomach, pancreas, bowels	2	1109 (220)	High	DA-EPOCHR	PD (CNS)

Table S1. Clinical features at diagnosis and primary therapy received for PMBCL patients with CNS relapse.

PS: performance status; LDH: lactate dehydrogenase; IPI: International Prognostic Index; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; DA-EPOCHR: dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; HD-MTX: high-dose methotrexate; IT MTX: intrathecal methotrexate; CNS central nervous system; PD progressive disease; CR complete remission; PR partial remission

Patient	Time to CNS relapse (years)	Site of relapse	Treatment for CNS Relapse	Outcome	Follow up from time of CNS relapse in alive patients (years)
1	4.74	Parenchymal	Dexamethasone only	Death (lymphoma)	N/A
2	0.70	Parenchymal	HD-MTX x 3; WBRT	CR	13.6
3	0.96	Leptomeningeal + paravertebral mass	Dexamethasone only	Death (lymphoma)	N/A
4	0.67	Parenchymal → mediastinum, lung	HD-MTX x 3; WBRT; GDP x 5, BuMelThiot ASCT	CR	8.2
5	1.29	Parenchymal, leptomeningeal	MTR x 4; WBRT, pembrolizumab; R-ICE x 3, BuMelThiot ASCT	CR	4.1
6	0.43	Parenchymal	MTR x 2; cytarabine x 1, WBRT, pembrolizumab	CR	2.1

Table S2. Characteristics, therapy and outcome of patients with CNS relapse

HD-MTX: high-dose methotrexate; WBRT: whole brain radiation therapy; GDP: gemcitabine, dexamethasone, cisplatin; BuMelThiot: busulfan, melphalan, thiotepa; ASCT: autologous stem cell transplant; MTR: high-dose methotrexate, temozolomide, rituximab; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; N/A: not applicable: CR complete remission

CNS-IPI risk factor	5 year risk of CNS relapse with risk factor (95% CI)	5 year risk of CNS relapse without risk factor (95% CI)	P-value
Renal and/or adrenal involvement	30.8% (8.7%, 56.6%)	1.1% (0.2%, 3.8%)	<0.00001
Age >60	11.3% (1.7%, 31.3%)	1.8% (0.6%, 4.3%)	0.033
Stage III or IV	5.2% (1.9%, 11.0%)	1.0% (0.1%, 5.1%)	0.026
Elevated LDH	3.8% (1.5%, 7.7%)	0	0.139
PS $\geq$ 2	5.1% (1.6%, 11.7%)	1.4% (0.3%, 4.4%)	0.142
Extranodal sites > 1	4.8% (1.5%, 10.9%)	1.7% (0.3, 5.5%)	0.098

Table S3. Cumulative risk of CNS relapse in PMBCL by the CNS-IPI risk factors (estimated using a competing risk approach)

CNS central nervous system; CI confidence interval

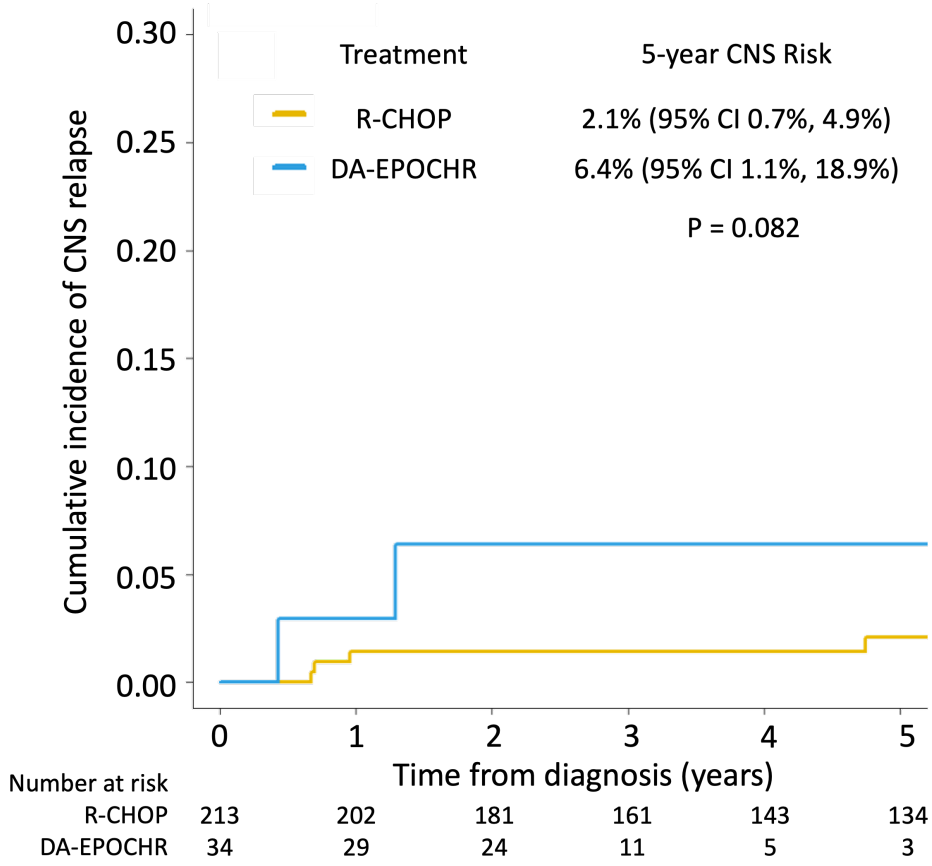


Figure S1. Cumulative incidence of CNS relapse in PMBCL by treatment with R-CHOP or DA-EPOCHR (estimated using a competing risk approach)

CNS: central nervous system; CI: confidence interval; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; DA-EPOCHR: dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab