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The number of extranodal sites assessed by PET/CT scan is a powerful predictor of CNS relapse for patients with diffuse large B-cell lymphoma: An international multicenter study of 1,532 patients treated with chemoimmunotherapy

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Abstract

Purpose: Development of secondary central nervous system involvement (SCNS) in patients with diffuse large B-cell lymphoma (DLBCL) is associated with poor outcomes. The CNS International Prognostic Index (CNS-IPI) has been proposed for identifying patients at greatest risk, but the optimal model is unknown.

Methods: We retrospectively analyzed patients with DLBCL diagnosed between 2001-2013, staged with PET/CT and treated with R-CHOP(-like) regimens. Baseline clinicopathologic characteristics, treatments, and outcome data were collected from clinical databases and medical files. We evaluated the association between candidate prognostic factors and modeled different risk models for predicting SCNS.

Results: Of 1,532 patients, 62 (4%) subsequently developed SCNS. By multivariate analysis, disease stage III/IV, elevated serum LDH, kidney/adrenal, and uterine/testicular involvement were independently associated with SCNS. There was a strong correlation between absolute number of extranodal sites and risk of SCNS; the 144 patients (9%) with >2 extranodal sites had a 3-year cumulative incidence of SCNS of 15.2% (95%CI 9.2-21.2%) compared with 2.6% (95%CI 1.7-3.5) among those with ≤2 sites (P<0.001). The 3-year cumulative risks of SCNS for CNS-IPI defined risk groups were 11.2%, 3.1%, and 0.4% for high, intermediate and low risk patients, respectively. All risk models analyzed had high negative predictive values, but only modest positive predictive values.

Conclusions: Patients with >2 extranodal sites or high-risk disease according to the CNS-IPI should be considered for baseline CNS staging. Clinical risk prediction models suffer from limited positive predictive ability, highlighting the need for more sensitive biomarkers to identify patients at highest risk of this devastating complication.

Highlights:

- Risk of CNS relapse in diffuse large B-cell lymphoma is predicted by the CNS-IPI
- The CNS-IPI remains valid in PET/CT staged diffuse large B-cell lymphoma
- More than two extranodal sites at diagnosis confers increased risk of CNS relapse

Keywords: Diffuse large B-cell lymphoma, PET/CT, CNS-IPI, CNS relapse, secondary CNS involvement, CNS prophylaxis, Prognosis

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Introduction

Patients with secondary CNS involvement (SCNS) by diffuse large B-cell lymphoma (DLBCL) have a dismal prognosis, highlighting the pressing need for effective preventative strategies.(1-11) The addition of CNS-penetrating chemotherapeutics such as high-dose methotrexate (HDMTX) into frontline protocols appears the most promising prophylactic strategy and has been recommended by recent guidelines.(10, 12, 13) Clinical risk factors for SCNS are well characterized and have been used to construct risk models, which allow targeted application of such prophylaxis.(2-4, 14, 15) The CNS-IPI, the best validated of these, combines established International Prognostic Index (IPI) risk factors (age >60 years, stage III/IV disease, >1 extranodal site, ECOG performance score >1, and LDH above upper normal limit) with kidney/adrenal involvement into a 6-point score with high-risk patients defined by a total score of ≥4.(16) Disease stage and extranodal involvement are consistent risk factors for SCNS in most analyses, but their association with SCNS may be influenced by the imaging modality used for baseline staging. In DLBCL, PET/CT detects more extranodal disease sites than conventional staging and this leads to upstaging in a relevant number of patients.(17) The aims of this study were to examine risk factors for SCNS, and validate the CNS-IPI model in a large independent cohort of PET/CT staged patients treated with R-CHOP or R-CHOP-like regimens

Patients and Methods

This retrospective study included patients from clinical databases (Guy's and St Thomas' Hospital [London] and Peter MacCallum Cancer Centre [Melbourne]) or from regional (British Columbia Cancer Agency [BCCA] Centre for Lymphoid Cancer Database [Vancouver BC]) and national (Danish Lymphoma Registry [LYFO]) lymphoma registries. Data collection was compliant with national and local regulations.

The patients were diagnosed with DLBCL between 2001 and 2013, but the surveyed time period varied between the centers according to the availability of PET/CT and database characteristics. Patients fulfilling the following criteria were included: a) treatment-naïve DLBCL, b) R-CHOP(-like) therapy, and c) staging with PET/CT. Baseline CNS staging

procedures varied according to site, however CNS imaging or cerebrospinal fluid (CSF) evaluation were not required for inclusion. Patients with known CNS involvement at the time of diagnosis (parenchymal, leptomeningeal, or intraocular) were excluded. Patients coincidentally diagnosed with discordant involvement of the bone marrow by a low-grade lymphoma during staging work-up for DLBCL were allowed in the study. Medical records and/or databases were reviewed for clinical characteristics and patient outcome. PET/CT reports were reviewed by a clinician investigator at each site for staging information. Multiple lesions within one organ or tissue type (i.e. multiple skeletal or hepatic lesions) were considered a single extranodal site. Bone marrow involvement was defined as focal lesions in the bone marrow on staging PET/CT and/or bone marrow biopsy positive for DLBCL.(18)

Patients treated with R-CHOP or similar regimens (R-CEOP [rituximab, cyclophosphamide, etoposide, vincristine, prednisone] and R-CHOEP [R-CHOP with etoposide]) were included. Radiotherapy and CNS prophylaxis were administered according to local policy in place at time. Common indications for radiotherapy included limited stage DLBCL in combination with abbreviated R-CHOP, bulky disease, or solitary extranodal lesions. The strategies for CNS prophylaxis included intrathecal chemotherapy (typically MTX ± cytarabine ± methylprednisolone), systemic high-dose antimetabolite therapy (MTX or cytarabine), or both intrathecal and systemic therapy. The indications cited for CNS prophylaxis included involvement of specific extranodal sites (including kidney/adrenal and testicular involvement), sites with anatomic proximity to the CNS, and elevated LDH in combination with advanced stage disease/extensive extranodal involvement. As evaluation of CNS prophyalxis was not the primary focus of the study, we did not collect information regarding doses or timing of CNS prophylaxis delivered. During the inclusion period, however, it was common practice to delivered IT prophalxis synchronously with R-CHOP(-like) treatment whereas systemic prophylaxis was given after completion of R-CHOP in many cases.

SCNS was defined as DLBCL relapse within the brain parenchyma, leptomeninges, spinal cord, or eye (intra-vitreous only). Pathological or cytological verification of SCNS was not mandatory in the presence of compatible clinical and radiologic findings.

Statistical analyses

Patient characteristics were summarized using descriptive statistics and compared using appropriate tests. Time to SCNS was defined as time from initial diagnosis of lymphoma to date of first SCNS. The cumulative incidence of SCNS was estimated using Fine and Gray's competing risk regression and death without SCNS was treated as a competing risk.(19) However, interpretating estimated effect parameters obtained in a Fine and Gray's approach as cause-specific SCNS risk is complicated and the effect of the covariates on the cause-specific hazard was estimated using Cox proportional hazards models with censoring of deaths before SCNS. The variables with P ≤0.15 in univariate analyses were entered in a multivariate Cox proportional hazards model. Increased risk of SCNS with uterine involvement by DLBCL was previously reported in an analysis of female patients in this cohort and was included in the Cox analyses to adjust for confounding.(20) The CNS-IPI risk model was compared with other models in explorative analyses. Risk of SCNS associated with international prognostic index (IPI) >2 was also included in this analysis.(21) Since there was overlap between the 86 BCCA patients included in the present study and those included in the CNS-IPI validation study, all BCCA patients were excluded from the validation of the CNS-IPI presented in this study.(16) The statistical programming language R version 3.2.2 was used for all statistical analyses.

Results

In total, 1,532 DLBCL patients were included (Denmark n=1088, BCCA n=86, Guy's and St Thomas' Hospital n=147, and Peter MacCallum Cancer Centre n=211). Baseline demographics and treatment information are shown in Table 1. With a median follow-up from diagnosis of 40 months, the 3-year PFS and OS rates were 72% (95% CI 70,75%) and 78% (95% CI 76,80%), respectively. Overall, 1520/1532 (99.2%) patients underwent staging bone marrow biopsy and 90 (5.9%) of those patients had morphologic bone marrow involvement by a low-grade lymphoma.

Sixty-two patients (4%) developed SCNS at a median of 9 months (range 2-78) from initial diagnosis (Figure 1A). SCNS occurred during first-line treatment in nine patients (15%), at first relapse 41 (66%) and at second or subsequent relapse in 12 (19%). At the time of SCNS, 20 (32%) also had systemic disease. SCNS was documented solely by CSF cytology

in 15 (24%), imaging in 36 (58%), both in 10 (16%) and one patient had intravitreal relapse. Among those with imaging documented SCNS without positive CSF, 18 (50%) had confirmatory brain biopsy; overall 69% of cases were histologically confirmed. Among the late SCNS events (>60 months after first pathologic diagnosis of DLBCL), 3/3 had biopsy documented SCNS.

The 3-year cumulative risk of SCNS according to specific clinicopathological features and the results of Cox analyses are shown in Table 2. In multivariate analysis, stage III/IV, elevated LDH, involvement of kidney/adrenal, and reproductive organs (uterus/testis) was significantly associated with SCNS. Infiltration by indolent lymphoma in the bone marrow was not associated with increased risk of SCNS.

The CNS-IPI risk group distribution is shown in Table 1. In an analysis excluding all patients from BCCA (previously included in another validation study(16)), the 3-year cumulative incidence of SCNS was 11% (95% CI 7,15%) in the high-risk group, 3% (95% CI 2,4%) in the intermediate-risk group, and 0.4% (95% CI 0,1%) in the low-risk group (Fig 1B).

Involvement of >1 extranodal site, as defined in the IPI score, was not an independent risk factor for SCNS in the patients included in the testing cohort of the recent CNS-IPI publication.(16) In an exploratory analysis, we analyzed the risk of SCNS associated with increasing number of extranodal sites detected on staging PET/CT (Figure 2A and Table 3). There was an incremental increase in the risk of SCNS with increasing total number of extranodal sites detected. According to the classifier performance curves (not shown), sensitivity and specificity were balanced using a cut-off >2 extranodal sites and the cumulative incidence of SCNS using this cut-off is shown in Figure 2B. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of different CNS risk models are presented in Table 4. The performance of the CNS-IPI risk model was tested against a simple model for SCNS using >2 extranodal sites, IPI>2, and the risk model proposed by Boehme *et al.* in Table 2.(3, 16) Relative to the CNS-IPI, the >2 extranodal sites model defined fewer patients as high-risk, had higher specificity and overall accuracy, but lower sensitivity. Among patients with >2 extranodal sites, 105/143 (73%) were also high-risk according to the CNS-IPI. For patients with >2 extranodal sites who did not met the CNS-IPI high-risk definition, 3/38 patients (8%) suffered SCNS. Among the three latter patients, none had kidney/adrenal or testis involvement, but one had uterine involvement by

DLBCL. The PPV was low (10-15%) for all tested models and the overall accuracy was poorest when using IPI>2 as the high-risk defining feature (Table 4). In an analysis including the clinicpathologic features independently associated with SCNS (Table 2), >2 extranodal sites remained independently associated with SCNS (HR 2.52 [95%CI 1.32,4.80] *P*=0.005). Among patients witth >2 extranodal sites, 6/78 men had testicular involvement and 34/144 of all had kidney involvement.

In a separate analysis of elderly DLBCL patients (>70 years), the 3-year cumulative incidence of SCNS in low, intermediate, and high-risk CNS-IPI were 0% (95%CI 0.0,0.0), 2.2% (95%CI 0.3,4.1), and 9.0% (95%CI 4.1,14.0), respectively. Thus, in elderly patients the CNS-IPI remained a valid tool for SCNS risk stratification.

Among CNS-IPI high-risk patients, 98/292 (33.6%) received CNS prophylaxis (26 systemic, 33 intrathecal, and 39 both). The cumulative incidences of SCNS for CNS-IPI high-risk patients treated with or without systemic CNS prophylaxis who attained at least a PR following first-line treatment (to avoid guarantee time bias) were similar (3-year SCNS rates were 11.2% (95%CI 10.8,11.6) for patients treated with systemic CNS prophylaxis +/- IT prophylaxis versus 10.2% (95%CI 10.0,10.3) for patients treated without systemic CNS prophylaxis, (log-rank test; P=0.84).

Discussion

This study highlights the role of PET/CT in identifying DLBCL patients at increased risk of SCNS after R-CHOP chemotherapy. In exploratory analysis of the SCNS risk associated with extranodal DLBCL, we observed a striking proportional correlation between the PET/CT-detected absolute number of extranodal sites of involvement and risk of SCNS. While the association between extranodal dissemination in DLBCL (>1 extranodal site) and SCNS has been reported,(8) the marked increase in risk with an increase in the absolute number of extranodal sites has not previously been reported to our knowledge. It is possible the increased risk of SCNS in patients featuring involvement of multiple extranodal sites may be driven by the presence of associated biological factors such as dual translocations of

MYC and *BCL2* rearrangements and/or *MYC/BCL2* co-expression, however, data on these variables were unavailable for the majority of patients in our study.(22)

We did not find an increased risk of SCNS among patients with involvement of breast or sinus/orbital structures, but our analyses may be biased, as 34/53 patients (64%) with sinus and/or orbital involvement and 7/35 patients (20%) with breast involvement received CNS prophylaxis. Consistent with our results, however, patients with craniofacial involvement undergoing immunochemotherapy in German trials did not have increased risk of SCNS.(23) Large cell involvement of the bone marrow may fall into a similar category: It was described in pre-rituximab series(8) to be a risk factor for SCNS, but data from rituximab treated patients are less concordant with some studies suggesting it remains a predictor(4) and others not.(24) Other specific extranodal sites of involvement such as the testis was not included in the CNS-IPI risk model despite data from large retrospective series comprised exclusively of patients with primary testicular lymphoma that indicated 5-year cumulative incidence of 19%.(25) This is likely explained by the under-representation of such patients in the population from which the original CNS-IPI was derived. Consistently, testicular involvement was associated with significantly increased risk of SCNS in multivariable analysis in the present study despite widespread use of CNS prophylaxis for this group of patients. Recent data suggests, that female reproductive organ involvement appears similarly associated with increased SCNS risk, although this is not consistently found in all study populations.(16, 20, 26, 27)

We compared the performance of several risk models in our cohort. The CNS-IPI was originally developed in patients treated on prospective clinical trial protocols, but has now been validated in two large independent cohorts comprising patients treated at both community and academic centers.(16) Consequently, the proportion of patients (263/2164 [12.1%]) in the original German study classified as high-risk (score 4-6) was substantially lower than in the two validation studies: 344/1597 (21.5%) in the BCCA cohort, and 276/1433 (19%) in the present study.(16) Nevertheless, the CNS-IPI has produced remarkably consistent risk estimates in three studies collectively including approximately 5,300 patients receiving chemoimmunotherapy, making it the most robust index developed to date. It also successfully predicted risk of SCNS in the elderly DLBCL patients (>70 years) in the present study. However, it has several limitations. In our cohort, a CNS-IPI score≥4

had excellent NPV (98%), moderate sensitivity (56%) and specificity (82%), but poor PPV (12%) raising concerns of overtreatment if selecting patients for systemic CNS prophylaxis based on this score alone. All risk models examined performed poorly in this regard: using a cut-off of >2 extranodal sites of involvement by PET we observed a PPV of 15% and specificity of 92% at the cost of reduced sensitivity (36%). Using the original IPI score (IPI score >2 as high-risk defining feature), the sensitivity was significantly better than other models, but the specificity was lower leading to problematic overtreatment if IPI>2 is used as indication for CNS prophylaxis. The difficulty of developing clinical useful models arises from the low incidence of SCNS and the relative low HR associated with individual risk factors. This emphasizes the need to identify and prospectively validate more precise biomarkers for SCNS to improve stratification of intermediate and high risk groups. However, the molecular, immunologic or cellular mechanisms underlying SCNS remain poorly understood. Geng *et al* performed a series of experiments using an integrated approach suggesting a possible role for B- and T-lymphocyte attenuator (*BTLA*) in mediating SCNS.(28) These observations, while intriguing, remain conjectural and require confirmation. Similar to CNS prophylaxis, applying rigorous baseline screening for CNS involvement in high-risk patients may also reduce the number of SCNS cases substantially. For example, the addition of flow-cytometry analysis of CSF increase the detection rate of discrete baseline CNS involvement by 6% in patients evaluated with lumbar puncture.(29)

We observed no significant difference in the crude rate of SCNS among the 61 CNS-IPI high-risk patients who received systemic CNS directed prophylaxis relative to the 155 patients who did not (3-year cumulative SCNS risk 11.2 vs. 10.2%, P=0.84 – only patients achieving at least PR included in this analysis). It is important to note that this study was not designed to assess the impact of CNS prophylaxis; as such, we did not collect detailed information regarding dose, schedule and timing. During the inclusion period, it was common practice many places to deliver systemic CNS prophylaxis after completing R-CHOP, but a recent prospective study suggest that early HDMTX interponated between the first R-CHOP cycles may reduce risk of SCNS substantially for younger high-risk patients.(30) Also, there were likely biases and confounding factors in why these patients were selected to receive such prophylaxis. Evidence regarding the efficacy of this modality are somewhat conflicting. Data from two studies, one retrospective(31) and one prospective (32) suggest the use of high-dose antimetabolites may not reduce SCNS. In contrast, data from several other

retrospective (7, 10, 13) and prospective (33) studies do suggest a risk reduction. Therefore, for patients with high risk CNS-IPI, involvement of specific high-risk sites, and possibly also those with >2 extranodal sites by PET/CT who do not fulfill other high-risk criteria, we continue to advocate systemic CNS prophylaxis be considered.

Our study has weaknesses. We did not perform central PET/CT or pathology review, and in most cases, immunohistochemical stains (MYC, BCL2, Ki-67) and fluorescence *in situ* hybridization for rearrangements in *MYC*, *BCL2* and *BCL6* were not performed. In many cases, PET/CT scans were jointly reviewed by nuclear medicine specialists and radiologists and consensus conclusions made. Given the multi-centre nature of the study and timespan included, we cannot provide the exact interpretation criteria used in each case. Baseline lumbar puncture and CNS imaging of the brain were also not routinely performed, thus, we cannot be exclude the possibility that a few SCNS patients had occult CNS disease at the time of initial diagnosis. The above limitations are shared by other large SCNS database studies.(3, 4, 16) Furthermore, information about HIV status was unavailable, although the populations included had low prevalence for HIV infection. Systemic CNS prophylaxis was used in 13% of the patients included in the present study. Although systemic CNS prophylaxis did not completely eliminate the risk of SCNS in the CNS-IPI high risk patients in our study, the inclusion of these patients may have affected the analysis. Nonetheless, our data reflect a real world population in which many patients with high CNS-IPI do routinely receive CNS-directed prophylaxis and thus still has relevance.

In conclusion, we have confirmed the robust ability of the CNS-IPI to predict CNS relapse in a large independent cohort of patients and demonstrated that the risk of CNS relapse increases proportionally with the absolute number of PET-detected extranodal sites. Patients with DLBCL and >2 extranodal sites may also be relevant for CNS staging and consideration of systemic prophylaxis, independent of CNS-IPI. This finding requires validation in an independent cohort.

Tables

Table 1: Clinic-pathological features of 1,532 patients with diffuse large B-cell lymphoma staged with PET/CT and treated with R-CHOP(-like) therapy.

Characteristic	***N* (%)**
Median age, years (range)	65 (17-92)
Male:female ratio	1.26
Ann Arbor Stage, *N* (%) • I • II • III • IV	 298 (19%) 275 (18%) 303 (20%) 656 (43%)
Extranodal sites, *N* (%) • 0 sites • 1 site • 2 sites • 3 sites • ≥4 sites	 590 (39%) 567 (37%) 231 (15%) 92 (6%) 52 (3%)
Elevated serum LDH, *N* (%)*	755 (49%)
B-symptoms, *N* (%)*	593 (39%)
R-IPI risk groups, *N* (%)* • Very good (score 0) • Good (score 1-2) • Poor (score 3-5)	 176 (12%) 729 (48%) 614 (40%)
CNS-IPI risk group, *N* (%)* • Low(score 0-1) • Intermediate(score 2-3) • High (score 4-6)	 513 (34%) 714 (47%) 292 (19%)
Frontline immunochemotherapy, *N* (%) • R-CHOP • R-CHOEP • R-CEOP	 1395 (91%) 105 (7%) 32 (2%)
Radiation therapy, *N* (%)	513 (34%)
CNS prophylaxis, *N* (%) • Systemic alone • Intrathecal alone • Systemic and intrathecal • None	 77 (5%) 129 (8%) 118 (8%) 1208 (79%)

*Patients with missing values: LDH = 11, B-symptoms = 24, R-IPI score = 13, and CNS-IPI score = 13.

Table 2: 3-year cumulative incidences for secondary CNS (SCNS) involvement and hazard ratio (HR) for SCNS associated with a variety of clinic-pathological features. Factors with P≤0.15 in univariate analyses were included in the multivariate analysis.

	Number of patients, n (%)	**3-yr Cumulative risk of SCNS, % (95%CI)**	**Univariate Analyses**		**Multivariate Analysis (95%CI)**	
			HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age > 60 years	971 (63%)	5 (3,6)	1.86 (1.05,3.29)	0.03	1.49 (0.82,2.70)	0.19
Stage III/IV disease	959 (63%)	6 (4,7)	13.33 (4.18,42.53)	<0.001	5.49 (1.6,18.92)	0.007
B-symptoms	593 (39%)	5 (3,7)	1.75 (1.05,2.90)	0.03	0.80 (0.46,1.37)	0.41
>1 extranodal site	375 (24%)	8 (5,11)	3.93 (2.39,6.47)	<0.001	0.94 (0.48,1.84)	0.86
Elevated serum LDH	766 (50%)	6 (5,8)	5.86 (2.97,11.54)	<0.001	3.94 (1.90,8.18)	<0.001
ECOG performance status >1	236 (15%)	6 (3,9)	1.96 (1.08,3.56)	0.03	1.02 (0.53,1.94)	1
Liver	129 (8%)	7 (3,12)	3.21 (1.71,6.03)	<0.001	1.80 (0.88,3.66)	0.11
Kidney/adrenal	64 (4%)	14 (6,23)	5.27 (2.68,10.38)	<0.001	3.36 (1.57,7.19)	0.002
Breast	35 (2%)	3 (0,9)	1.43 (0.35,5.85)	0.62		
Sinus	42 (3%)	8 (0,16)	1.78 (0.56,5.68)	0.33		
Bone marrow#	437 (29%)	7 (4,9)	2.99 (1.81,4.92)	<0.001	1.47 (0.83,2.59)	0.18
Discordant bone marrow#	90 (6%)	4 (0,8)	0.89 (0.28,2.84)	0.84		
Testis	48 (6%)*	7 (0,15)	2.55 (0.87,7.53)	0.10	5.15 (1.61,16.53)	0.003
Uterus	17 (3%)*	41 (17,66)	16.41 (6.13,43.90)	<0.001	15.68 (5.03,48.88)	<0.001
Thyroid	35 (2%)	11 (1,22)	3.18 (1.15,8.76)	0.03	2.30 (0.79,6.70)	0.13
Orbits	23 (2%)	5 (0,14)	1.14 (0.16,8.23)	0.9		

#Bone marrow involvement ascertained by focal lesions on PET/CT and/or bone marrow biopsy (only DLBCL). Discordant bone marrow involvement was defined as infiltration by an indolent lymphoma diagnosed at the time of DLBCL.

* Number of patients with uterus or testis involvement is relative to the male and female cohorts, respectively.

Table 3: Relationship between number of extranodal disease sites and risk of secondary CNS involvement.

Number of extranodal sites, n	Number of patients, n (%)	3-year cumulative risk of SCNS, % (95% CI)	Univariate analysis, HR (95% CI)	Multivariate analysis, HR (95% CI)
0	590 (39%)	2 (0,3)	1 (ref)	1 (ref)
1	567 (37%)	3 (2,5)	3.03 (1.35,6.81)	2.97 (1.26,7.00)
2	231 (15%)	4 (1,6)	3.64 (1.44,9.24)	1.54 (0.52,4.60)
3	92 (6%)	9 (3,15)	9.65 (3.71,25.07)	3.59 (1.14,11.30)
≥4	52 (3%)	25 (13,38)	25.80 (10.67,62.37)	11.37 (3.77,34.25)

*Multivariate analysis including adjustment for elevated LDH, age>60 years, and ECOG performance>1. Stage III/IV disease and kidney/adrenal disease was not included due to their intrinsic relationship with extranodal disease.

Table 4: Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of different CNS relapse risk models and >2 extranodal sites.

	CNS-IPI High risk	ECOG performance>1 + >1 extranodal site + elevated LDH (Boehme et al.) (3)	P*	>2 extranodal sites	P*	>2 IPI	P*
Proportion of high risk patients	292/1519 (19.2%)	84/1519 (5.5%)	<0.001	144/1532 (9.5%)	<0.001	614/1519 (40.4%)	<0.001
SCNS according to risk							
• High risk	34/292 (11.6%)	9/84 (10.7%)	1	22/144 (15.3%)	0.29	46/614 (7.5%)	0.045
• Non-high risk	27/1227 (2.2%)	52/1435 (3.6%)	0.039	40/1388 (2.9%)	0.32	15/905 (1.7%)	0.43
Sensitivity (95% CI)	55.7 (42.4,68.5)	14.8 (7.0,26.2)	<0.001	35.5 (23.7,48.7)	0.005	75.4 (62.7,85.5)	<0.001
Specificity (95% CI)	82.3 (80.2,84.2)	94.9 (93.6,95.9)	<0.001	91.7 (90.2,93.1)	<0.001	61 (58.5,63.6)	<0.001
Positive predictive value (95% CI)	11.6 (8.2,15.9)	10.7 (5.0,19.4)	0.75	15.3 (9.8,22.2)	0.1	7.5 (5.5,9.9)	<0.001
Negative predictive value (95% CI)	97.8 (96.8,98.5)	96.4 (95.3,97.3)	<0.001	97.1 (96.1,97.9)	0.04	98.3 (97.3,99.1)	0.07
Accuracy (95% CI)	81.2 (79.2,83.2)	91.6 (90.1,93.0)	<0.001	89.4 (87.8,90.9)	<0.001	61.6 (59.1,64.1)	<0.001

*P values reflect comparisons of model by Boehme at al. and >2 extranodal sites model to the CNS-IPI model.

Conflict of Interest

The authors report no conflicts of interests

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