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Location matters in early stage nodal diffuse large B-cell lymphoma

K Lontos¹, A Tsagianni², JM Yuan³, D Normolle⁴, M Boyiadzis¹, JZ Hou¹, SH Swerdlow⁵, KA Dorritie¹

¹UPMC, Division of Hematology/Oncology, Pittsburgh, PA, USA

²UPMC, Division of Internal Medicine, Pittsburgh, PA, USA

³Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

⁴UPMC Hillman Cancer Center, Biostatistics Facility, Pittsburgh, PA, USA

⁵UPMC, Department of Pathology, Division of Hematopathology

Dear Editor,

Diffuse large B-cell lymphoma (DLBCL) is the most common type of B-cell lymphoma in the United States[1]. The introduction of rituximab has significantly improved outcomes in the treatment of DLBCL[2]. However, relapsed and refractory cases still pose a challenge, with only 20% surviving at 2 years[3]. While early stage patients generally have a more favorable prognosis, about 30% of Stage I and II patients will still relapse[4]. It is therefore critical to determine factors that may better predict for relapse and/or chemotherapy resistance in order to aid in treatment decisions. More recently, our understanding of the biology of DLBCL has evolved such that assessment of molecular risk through evaluation of the cell of origin and specific genetic mutations are being incorporated into prognostication and clinical decision making[5]. However, while the location of extranodal involvement has been implicated in the prognosis[6], the location of nodal DLBCL has not been investigated as a prognostic factor. We aimed to evaluate the relationship between location of lymphadenopathy and outcome in early stage DLBCL patients.

Our study was based on the Surveillance, Epidemiology, and End Results (SEER) database and the National Cancer Database (NCDB). The SEER database collects information on cancer incidence and survival from 18 registries (Alaska Native Tumor Registry, Arizona Indians, Cherokee Nation, Connecticut, Detroit, Georgia Center for Cancer Statistics, Greater Bay Area Cancer Registry, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Seattle-Puget Sound, Utah). It covers approximately 28% of the current US population based on the 2010 census[7]. The SEER data are de-identified and available to the public for research purposes. The NCDB is a database sponsored by the American College of Surgeons and the American Cancer Society. It collects hospital registry data from more than 1,500 Commission on Cancer (CoC)-accredited facilities. It captures about 70% of the newly-diagnosed cancer cases in the nation[8]. Although it is likely that these two databases share cases, the extent of this overlap has not been investigated[9].

Both databases were used to extract cases of DLBCL from 2001 to 2014 using the ICD-O-3 code 9680 (malignant lymphoma, large B-cell, diffuse, NOS). Patients with primary mediastinal B cell lymphoma are coded as 9679/3 based on ICD-O-3 so they were not included in the analysis. 124,934 cases from NCDB and 75,305 cases from SEER were identified. Only stage I and stage II cases with a defined nodal location were included. Stage II cases involving two different location sites are marked with the ICD-O-3 C77.8 code in the databases (Lymph nodes of multiple regions) and were excluded. The stage II cases involving bilateral lymph nodes of the same location, as per published guidelines[10], were included. 2001 was used as the date of inclusion as rituximab was approved initially in 1997 and the results of the study conducted by Groupe d'Etude des Lymphomes de l'Adulte was first presented as an abstract in December 2000 at the American Society of Hematology annual meeting[11]. The databases consider spleen and Waldeyer's Ring (WR) as nodal, so they were included in the extraction. Cases without follow-up, with unknown Ann-Arbor staging, unknown treatment data, unknown sex or race, with development of DLBCL after a previous malignancy, and without histologic confirmation of the disease were excluded. Survival curves were estimated by the Kaplan-Meier method. A Cox proportional hazard model was constructed to calculate the hazard ratios (HR) of overall survival for each of 7 specific locations (Head, Face and Neck, Axilla, Thoracic, Spleen, Abdomen, Pelvis, Inguinal) compared with Waldeyer's Ring (WR). The Cox proportional hazard model also included age (categorized into the following groups: 20–39, 40–59, 60–75, and >75 years), stage (I or II), gender (male or female), race (white, black, or other), and administrations of chemotherapy (No or Yes), radiation (No or Yes) and cancer-directed surgery (No or Yes). A pairwise comparison was performed. Proportionality was tested with Schoenfeld residuals. The likelihood ratio test was used to evaluate if the addition of the location to the Cox model improved the concordance of the model. Statistical analysis was performed with R v3.4. All *P* values presented are two-sided. For the Cox model *P* values less than .05 were considered statistically significant whereas for the pairwise comparison *P* values less than .007 (.05/7 tests) were considered statistically significant after the *Bonferroni* correction.

A total of 10,456 cases from SEER and 19,606 cases from NCDB were included in the analysis after the above inclusion criteria were applied (64,849 cases from SEER and 105,328 cases from NCDB did not meet the inclusion criteria, the majority of them because of advanced stage disease). The clinical and demographic characteristics of the cases are presented in Table 1. The majority of these cases were located in the Head, Face & Neck (HFN) and the abdomen. Most of the patients were white, 40–75 years-old, had stage I disease, and received chemotherapy but not surgery or radiation.

The survival analysis yielded similar results between the two databases. The Kaplan-Meier curves are presented in Figure 1, the results of the Cox model are presented in Table 2 and the results of the pairwise comparison are presented in Table 3. WR was shown to carry the best prognosis whereas abdomen and pelvis the worst. Axillary and inguinal location carry intermediate prognosis. The survival of HFN and spleen cases is between WR and axillary/inguinal whereas the prognosis of thoracic disease is between axillary/inguinal and abdomen/pelvis. The location of lymphadenopathy was important for the concordance of the model ($p < .001$) in both databases. In a post-hoc analysis, patients who were diagnosed with

DLBCL in the thorax were found to be much younger than all other patients combined (SEER 41% vs 11% in 20–39 years, $p < .001$, NCDB 38% vs 11%, $p < .001$).

This study demonstrates a statistically significant difference in survival for patients with nodal DLBCL based on the primary location of their disease across two very large databases. While molecular, cytogenetic and phenotypic data were not available for review, it is possible that lymphomas originating in the abdomen, pelvis or thorax exhibit a more high-risk gene signature. Likewise, it is known that WR cases likely include at least some cases of large B-cell lymphoma with *IRF4* rearrangement which portends a more favorable prognosis[12]. Additionally, regardless of staging, the initial volume of disease might have been higher in the thorax and abdomen/pelvis cases given that they were likely detected later. The thoracic location had discrepancies in results derived from the Cox model which showed poor prognosis after adjustment for multiple variables including age compared with the unadjusted Kaplan-Meier curve which showed better survival than all locations of DLBCL after 5–10 years of diagnosis. These discrepancies were largely because of the young age of the patients with thoracic disease as described above.

The strength of our study is the very large number of patients from two multi-institutional databases that cover the majority of the US population. Unfortunately, these databases do not capture details about the type of chemotherapy that was administered, duration of chemotherapy, staging tools, laboratory values (ie LDH), performance status, phenotypic features and cytogenetic or molecular alterations. Due to this limitation, we chose to present the results from both databases instead of building a prognostic model for validation. Furthermore, the results of the Cox model for chemotherapy, surgery and radiation should be interpreted with caution as this study is retrospective and very prone to treatment selection bias. Finally, our analysis relies on accurate reporting of the disease location which due to lack of centralized review might have been compromised.

The goal of our study was to highlight the differences in outcome among early stage DLBCL patients based on location of their disease. We hope that our results lead to prospective studies further exploring our observations and the potential incorporation of the location of lymphadenopathy into new prognostic scoring systems for early stage DLBCL.

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Figure 1.
Kaplan-Meier curves of overall survival for patients with diffuse large B-cell lymphoma from the SEER database (n = 10456) and the NCDB database (n = 19606).

Table 1:

Clinical and demographic characteristics of patients with diffuse large B-cell lymphoma from the SEER (n = 10456) and the NCDB (n = 19606) database.

Characteristic	Subgroup	SEER (%)	NCDB (%)
Site	WR	921 (9%)	1444 (7%)
	HFN	3276 (31%)	6230 (32%)
	Axilla	821 (8%)	1516 (8%)
	Inguinal	1072 (10%)	1990 (10%)
	Spleen	475 (5%)	837 (4%)
	Thorax	1296 (12%)	2652 (14%)
	Abdomen	2370 (23%)	4398 (22%)
	Pelvis	225 (2%)	539 (3%)
Sex	Male	5565 (53%)	10351 (53%)
	Female	4891 (47%)	9255 (47%)
Race	White	8861 (85%)	17355 (89%)
	Black	740 (7%)	1391 (7%)
	Other	855 (8%)	860 (4%)
Age	20–39	1169 (11%)	2210 (11%)
	40–59	3098 (30%)	5849 (30%)
	60–75	3530 (34%)	6730 (34%)
	>75	2659 (25%)	4817 (25%)
Stage	I	6628 (63%)	11228 (57%)
	II	3828 (37%)	8378 (43%)
Surgery	Yes	4281 (41%)	5554 (28%)
	No	6175 (59%)	14052 (72%)
Radiation	Yes	3406 (33%)	6702 (34%)
	No	7050 (67%)	12904 (66%)
Chemotherapy	Yes	8059 (77%)	16617 (85%)
	No	2397 (23%)	2989 (15%)

SEER, Surveillance Epidemiology and End Results; NCDB, National Cancer Database; WR, Waldeyer's Ring; HFN, Head Face & Neck

Table 2:

Cox proportional hazards model for overall survival in patients with diffuse large B-cell lymphoma from the SEER (n = 10456) and NCDB (n = 19606) databases. Multivariable analysis including location, sex, race, age, stage, surgery or not, radiation or not, chemotherapy or not.

Variable	SEER			NCDB		
	HR	95% CI	P value	HR	95% CI	P value
<i>Location</i>						
WR	-	-	-	-	-	-
HFN	1.18	1.02 – 1.37	.026	1.15	1.02 – 1.30	.023
Axilla	1.35	1.13 – 1.60	< .001	1.39	1.21 – 1.61	< .001
Inguinal	1.34	1.13 – 1.58	< .001	1.28	1.11 – 1.47	< .001
Spleen	1.24	1.01 – 1.52	.044	1.24	1.05 – 1.47	.011
Thorax	1.54	1.29 – 1.83	< .001	1.52	1.32 – 1.75	< .001
Abdomen	1.64	1.42 – 1.91	< .001	1.58	1.40 – 1.79	< .001
Pelvis	2.04	1.62 – 2.57	< .001	1.76	1.48 – 2.09	< .001
<i>Sex</i>						
Female	-	-	-	-	-	-
Male	1.18	1.1 – 1.26	< .001	1.19	1.13 – 1.25	< .001
<i>Race</i>						
Black	-	-	-	-	-	-
White	0.67	0.59 – 0.77	< .001	0.72	0.65 – 0.79	< .001
Other	0.69	0.58 – 0.82	< .001	0.60	0.50 – 0.71	< .001
<i>Age</i>						
20–39	-	-	-	-	-	-
40–59	2.11	1.71 – 2.61	< .001	1.82	1.56 – 2.13	< .001
60–75	4.60	3.74 – 5.65	< .001	3.67	3.16 – 4.26	< .001
>75	11.89	9.68 – 14.61	< .001	10.36	8.93 – 12.02	< .001
<i>Stage</i>						
I	-	-	-	-	-	-
II	1.23	1.15 – 1.32	< .001	1.25	1.19 – 1.32	< .001
<i>Surgery</i>						
No	-	-	-	-	-	-
Yes	0.83	0.77 – 0.89	< .001	0.75	0.71 – 0.80	< .001
<i>Radiation</i>						
No	-	-	-	-	-	-
Yes	0.68	0.63 – 0.74	< .001	0.66	0.62 – 0.70	< .001
<i>Chemotherapy</i>						
No	-	-	-	-	-	-
Yes	0.49	0.46 – 0.53	< .001	0.40	0.37 – 0.42	< .001

SEER, Surveillance Epidemiology and End Results; NCDB, National Cancer Database; HR, Hazard Ratio; CI, Confidence Intervals; WR, Waldeyer's Ring; HFN, Head Face & Neck

Table 3:

Results of the pairwise comparison of prognostic significance for OS between different locations after adjusting for sex, race, age, stage, surgery or not, radiation or not, chemotherapy or not. * indicates the *P* values that reached < 0.007 (*Bonferroni* correction) only in the SEER database, ** indicates the *P* values that reached < 0.007 only in the NCDB database whereas *** indicates the *P* values that reached < 0.007 in both databases.

	WR	HFN	Axilla	Inguinal	Spleen	Thorax	Abdomen	Pelvis
WR			***	***		***	***	***
HFN			**			***	***	***
Axilla	***	**					*	***
Inguinal	***					**	***	***
Spleen							***	***
Thorax	***	***		**				
Abdomen	***	***	*	***	***			

OS, Overall Survival; SEER, Surveillance Epidemiology and End Results; NCDB, National Cancer Database; WR, Waldeyer's Ring; HFN, Head Face & Neck