RESEARCH ARTICLE

Sites of extranodal involvement are prognostic in patients with diffuse large B-cell lymphoma in the rituximab era: An analysis of the Surveillance, Epidemiology and End Results database

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Approximately a third of the patients with diffuse large B-cell lymphoma present with extranodal involvement. Our study aims to identify primary extranodal sites of disease associated with prognosis in patients with diffuse large B-cell lymphoma (DLBCL) in the rituximab era. A secondary objective is to describe epidemiological and clinical characteristics of patients with extranodal DLBCL. We included adult patients from the Surveillance, Epidemiology and End Results (SEER) database (2004–2009) in whom DLBCL was the first malignancy diagnosed. Extranodal primary sites were divided into 12 groups according to the topography code reported by SEER. Multivariate overall survival (OS) analyses were performed using Cox proportional-hazard regression models adjusted for age, sex, race, and stage. From a total of 25,992 adult DLBCL patients included in our analysis, 32% presented with extranodal primary sites. Gastrointestinal tract (34%), head/neck (H&N; 14%), and skin/soft tissue (11%) were the most common. In comparison with nodal DLBCL, patients with extranodal involvement were older (with exception of skeletal sites) and presented with earlier stages. In the multivariate analysis, sites associated with worse OS rates were gastrointestinal (Hazard ratio (HR) 1.24, 95% confidence interval (CI) 1.15–1.33; P <0.001), pulmonary (HR 1.59, 95% CI 1.38–1.83; P <0.001), and liver/pancreas (HR 1.58, 95% CI 1.35–1.85; P <0.001), whereas H&N was associated with better survival (HR 0.79, 95% CI 0.70–0.89; P <0.001). In this population-based study, primary extranodal sites of involvement are associated with distinct outcomes in patients with DLBCL. Gastrointestinal, pulmonary, and liver/pancreas sites had a significant worse outcome than nodal sites.
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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma subtype accounting for approximately 30% of all the cases [1]. DLBCL is a clinically, pathologically, and molecularly heterogeneous entity. A reflection of such heterogeneity is the wide variation in outcomes among patients with DLBCL with 5-year survival times ranging between 30 and 80%. The most commonly used prognostic tool in patients with DLBCL is the International Prognostic Index (IPI) score, which has shown to be of utility in the modern, post-rituximab era [2]. One of the factors included in the IPI score is the number of extranodal sites [3]; having more than one extranodal site of involvement is considered a poor prognostic indicator. There are few studies, however, that have focused on evaluating the prognostic value of the primary extranodal site of origin itself.

There is mounting evidence that specific sites of involvement such as the Waldeyer ring could be associated with improved outcome [4,5]. On the other hand, other sites such as breast or testicular involvement have been associated with a worse prognosis [6,7]. Most of such reports are single-institution experiences without a comparative group or population-based studies with small sample sizes. We hypothesized that there could be clinical differences depending on the site of involvement in patients with DLBCL. Furthermore, specific extranodal sites might be associated with either a worse or a better outcome when compared with patients with nodal involvement.

The main objective of our study was to evaluate the clinical characteristics and potential prognostic value of the primary extranodal sites of involvement in the rituximab era in patients with DLBCL recorded in the United States (US) Surveillance, Epidemiology and End Results (SEER) database. A secondary objective is to describe the demographic and clinical characteristics of patients with extranodal DLBCL and compare them with the characteristics of patients with nodal DLBCL.

Additional Supporting Information may be found in the online version of this article.

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Patients and Methods

Data source and cohort selection

Our study was based on data from the SEER program database [8]. SEER collects cancer incidence, treatment, and survival information from 18 geographic areas in the United States, representing 28% of the entire population. We used direct case listings extracted by SEER*Stat software [9]. Our query included patients with a diagnosis of lymphoma with the International Classification of Diseases for Oncology, 3rd edition, ICD-O-3 histology code 9680 (diffuse large B-cell lymphoma, not otherwise specified) until December 31, 2009—the latest follow-up recorded in the SEER submission used for this study ($n = 85,613$). We excluded patients if they were diagnosed before 2004 ($n = 46,457$). The choice of this cutoff was motivated by our intent to study outcomes in patients treated with rituximab-containing regimens. Rituximab was approved by the US Food and Drug Administration for treatment of DLBCL in 2006; however, studies of practice patterns indicate that already in 2002, 79% of Medicare beneficiaries with DLBCL were receiving rituximab with anthracycline-based regimens for initial therapy [10]. We also excluded patients in whom DLBCL was a nonprimary malignancy ($n = 9,488$), if age at diagnosis was <20 years ($n = 733$), if the diagnosis was made by autopsy or death certificate only ($n = 144$), and if the primary site of the lymphoma was central nervous system (CNS; $n = 2,431$), mediastinum ($n = 255$) or unknown ($n = 105$). Primary CNS and primary mediastinal large B-cell lymphomas were excluded as the characteristics and outcomes of those cases are distinct. Primary CNS lymphoma has no defined staging system and is not typically treated with chemoimmunotherapy. Primary mediastinal large B-cell lymphoma is now recognized as a separate entity in the WHO classification and is recorded using a different ICD-O-3 histology code (9679). Our final study cohort included 25,992 individuals.

Definition of variables

The database contains variables indicating age at diagnosis, year of diagnosis, sex, race/ethnicity, clinical stage, primary site of involvement, outcome, survival time, and cause of death. Age was divided into eight categories (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and 90+ years), stage into early (Ann Arbor Stage I/II) and advanced (III/IV), sex into male and female, and race/ethnicity into White, Black, Hispanic, and Other. Primary site was categorized into 12 sites according to the ICD-O-3 topography code reported by SEER: breast, hematologic system (i.e., spleen, blood, and bone marrow), gastrointestinal (GI) tract, genitourinary (GU) tract, head and neck (H&N), liver/pancreas, lymph nodes, pulmonary system, skeletal tissue, skin/soft tissue, thyroid, and other sites (peritoneum, adrenal gland, heart, orbital, and not otherwise specified). Overall survival (OS) was the outcome of interest. OS was calculated as the time in months elapsed between the date of diagnosis and the date of death, date last known to be alive, or date of the study cutoff.

TABLE I. Primary Sites of Involvement of 25,992 Patients with a Diagnosis of Diffuse Large B-Cell Lymphoma from the SEER Database (2004–2009)

Primary site	Number	% Total cases	% Extranodal
Lymph nodes	17,788	68.4	–
Extranodal	8,204	31.6	100.0
Gastrointestinal tract	2,785	10.7	34.0
Head and neck	1,115	4.3	13.6
Skin and soft tissue	867	3.3	10.6
Genitourinary tract	685	2.6	8.4
Skeletal tissue	548	2.1	6.7
Respiratory system	456	1.8	5.6
Hematologic system	451	1.7	5.5
Liver/pancreas	417	1.6	5.1
Thyroid gland	311	1.2	3.8
Breast tissue	254	1.0	3.1
Other	315	1.3	3.9

Statistical analysis

Descriptive statistics with Chi-square tests were used to study differences between categorical variables. OS estimates were calculated using the Kaplan-Meier method. Multivariate Cox proportional-hazard regression models adjusting for confounding variables (age, sex, race, and stage) were fitted to evaluate the prognostic value of each extranodal site of involvement using the lymph node group as comparator. Given the multiplicity of pairwise comparisons within the database and the size of the database, we used a Bonferroni correction to minimize Type I error (i.e., falsely positive results) A P value <0.004 (i.e., P <0.05/12 primary sites) was considered statistically significant. All tests are reported with two-tailed P values and 95% confidence intervals (CI). Calculations and graphs were obtained using Stata, version 12.1 (StataCorp LP, College Station, TX).

Results

Characteristics of the population

We analyzed 25,992 patients >20 years with a diagnosis of DLBCL included in the SEER database between 2004 and 2009. The median age was 66 years (range: 20–105 years), and 63.5% of the patients were older than 60 years. The male-to-female ratio was 1.15:1. Racial distribution was as follows: White 71.3%, Hispanic 12.9%, Black 7.7%, and Other 8.1% of the population. Advanced clinical stage was seen in 51.6%. A total of 8,204 patients of this cohort had primary extranodal site at diagnosis (31.6%). The most common extranodal sites of involvement were GI tract, H&N, and skin/soft tissue (Table I).

Characteristics of the population according to the primary site of diagnosis

The complete characteristics of patients with DLBCL according to 12 primary sites are shown in Table II. All comparisons were made against nodal sites. With regard to age, patients >60 years accounted for 62% of the cases with lymph node sites. All extranodal sites were associated with higher proportion of patients >60 years, with

TABLE II. Clinical Characteristics of 25,992 Patients with a Diagnosis of Diffuse Large B-Cell Lymphoma from the SEER Database (2004–2009)

	Age ≥60		Male sex		Advanced stage		Race/ethnicity				
							White	Black	Hispanic	Other	
Primary site	N (%)	P	N (%)	P	N (%)	P	N (%)	N (%)	N (%)	N (%)	P
Lymph nodes	11,009 (62)	–	9,462 (53)	–	10,222 (61)	–	12,569 (71.2)	1,420 (8.0)	2,302 (13.0)	1,362 (7.7)	–
Gastrointestinal tract	1,899 (68)	<0.001	1,644 (59)	<0.001	857 (33)	<0.001	1,806 (65.2)	210 (7.6)	460 (16.6)	294 (10.6)	<0.001
Head and neck	767 (69)	<0.001	581 (52)	0.48	218 (21)	<0.001	782 (70.6)	88 (8.0)	125 (11.3)	112 (10.1)	0.02
Skin and soft tissue	602 (69)	<0.001	458 (53)	0.83	194 (24)	<0.001	678 (79.2)	49 (5.7)	87 (10.2)	42 (4.9)	<0.001
Genitourinary tract	470 (69)	<0.001	462 (67)	<0.001	207 (31)	<0.001	485 (71.4)	49 (7.2)	69 (10.2)	76 (11.2)	0.002
Skeletal tissue	285 (52)	<0.001	290 (53)	0.9	181 (34)	<0.001	420 (77.1)	41 (7.5)	61 (11.2)	23 (4.2)	0.006
Respiratory system	316 (69)	0.001	218 (48)	0.02	223 (50)	<0.001	356 (78.1)	36 (7.9)	33 (8.3)	26 (5.7)	0.005
Hematologic system	299 (66)	0.06	247 (55)	0.51	190 (47)	<0.001	349 (78.3)	27 (6.1)	42 (9.4)	28 (6.3)	0.01
Liver and pancreas	257 (62)	0.91	262 (63)	<0.001	206 (47)	<0.001	288 (69.2)	37 (8.9)	60 (14.4)	31 (7.5)	0.75
Thyroid gland	210 (68)	0.04	94 (30)	<0.001	38 (13)	<0.001	248 (81.1)	4 (1.3)	32 (10.5)	22 (7.2)	<0.001
Breast tissue	177 (70)	0.01	9 (4)	<0.001	45 (20)	<0.001	183 (73.2)	14 (5.6)	28 (11.2)	25 (10.0)	0.23
Other	205 (65)	0.25	165 (52)	0.78	95 (31)	<0.001	228 (72.8)	15 (4.8)	32 (10.2)	38 (12.1)	0.003

Race was unrecorded in 195 patients (0.8%). P values <0.004 were considered statistically significant.

TABLE III. Univariate and Multivariate Analysis of Prognostic Factors for Overall Survival in 25,992 Patients with Diffuse Large B-Cell Lymphoma from the SEER Database (2004–2009)

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	P	HR (95% CI)	P
Age				
20–29 years	Ref.		Ref.	
30–39 years	1.32 (1.05–1.67)	0.02	1.37 (1.08–1.74)	0.009
40–49 years	1.77 (1.43–2.19)	<0.001	1.78 (1.44–2.21)	<0.001
50–59 years	1.87 (1.52–2.30)	<0.001	1.94 (1.57–2.39)	<0.001
60–69 years	2.37 (1.93–2.90)	<0.001	2.52 (2.04–3.10)	<0.001
70–79 years	3.58 (2.93–4.38)	<0.001	3.95 (3.22–4.86)	<0.001
80–89 years	6.25 (5.11–7.64)	<0.001	7.11 (5.78–8.75)	<0.001
90+ years	9.99 (8.04–12.4)	<0.001	12.6 (10.1–15.8)	<0.001
Sex				
Female	Ref.		Ref.	
Male	0.99 (0.95–1.04)	0.74	1.16 (1.11–1.21)	<0.001
Race				
White	Ref.		Ref.	
Black	1.18 (1.09–1.27)	<0.001	1.64 (1.51–1.78)	<0.001
Hispanic	1.05 (0.99–1.12)	0.11	1.30 (1.22–1.39)	<0.001
Other	1.00 (0.93–1.09)	0.93	1.08 (0.99–1.17)	0.09
Stage				
Early	Ref.		Ref.	
Advanced	1.89 (1.82–2.00)	<0.001	1.95 (1.87–2.05)	<0.001

HR, hazard ratio; CI, confidence interval.

exception of skeletal sites (52%). With regards to sex, 54% of the patients with nodal primary sites were men. Male patients comprised a larger proportion in DLBCL with GU tract (67%), liver/pancreas (63%), and GI tract (59%), whereas a smaller proportion was seen in breast (4%) and thyroid (30%). With regard to stage, all extranodal primary sites were more likely to present with early stage. Comparisons according to race and primary site of involvement are also shown in Table II.

Survival analysis

The median OS of the entire cohort was 60 months with a 5-year OS of 50%. We used age, sex, race, and stage to construct our multivariate hazard model. Age >60, male sex, Hispanic race, Black race, and advanced stage were associated with a worse prognosis (Table III). We then proceeded to evaluate the prognostic value of the individual extranodal primary sites. In the multivariate analysis, after adjusting for age, sex, race, and stage, H&N sites were associated with a better prognosis and GI tract, liver/pancreas, and respiratory tract sites were associated with a worse prognosis (Fig. 1). When evaluating patients with Stage I/II disease only, gastrointestinal, pulmonary, and liver/pancreas sites retained remained significantly associated with survival, whereas H&N sites did not (Fig. 2). Complete survival analyses are shown in Table IV. A sensitivity analysis was performed in patients younger than 80 years with all stages ($n = 20{,}873$) and in patients younger than 80 with localized disease ($n = 9{,}538$). Such analyses also showed an adverse prognostic value for GI tract, liver/pancreas, and respiratory tract (See supplementary Table 5). H&N sites were associated with a better prognosis in all stage but did not retain statistical significance in localized disease (See supplementary Table 5).

Discussion

To the best of our knowledge, this is the first large population-based study evaluating the prognostic role of extranodal site of involvement on survival in patients with DLBCL in the rituximab era. In this context, the SEER database provides a real-world setting that

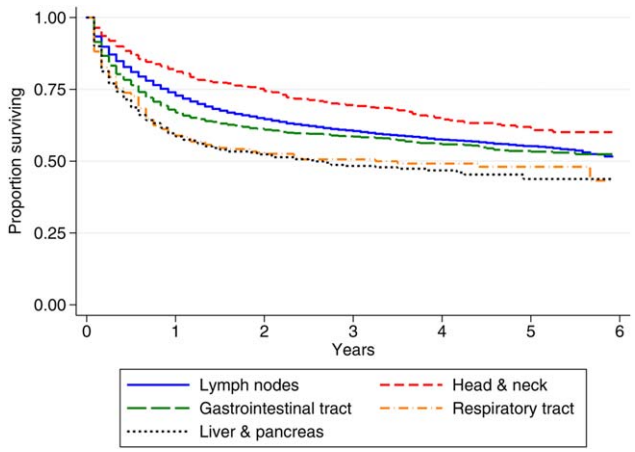

Figure 1. Kaplan Meier overall survival estimates for nodal, head & neck, gastrointestinal tract, liver & pancreas, and respiratory tract involvement in patients with diffuse large B-cell lymphoma from the SEER database, 2004–2009 (all stages). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

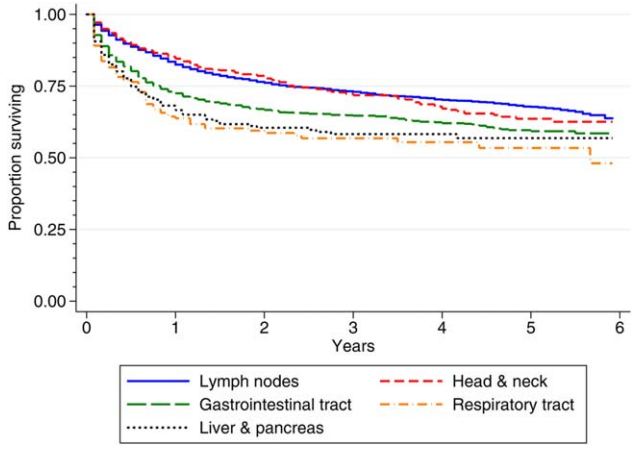

Figure 2. Kaplan Meier overall survival estimates for nodal, head & neck, gastrointestinal tract, liver & pancreas, and respiratory tract involvement in patients with diffuse large B-cell lymphoma from the SEER database, 2004–2009 (stages I and II). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

permits the study of the association between specific sites of involvement by DLBCL and clinical characteristics and outcomes. Our study demonstrates that specific sites of involvement are associated with either a better or a worse prognosis after adjusting for substantial confounders such as age, sex, race, and stage. Furthermore, specific extranodal sites of involvement by DLBCL are associated with distinct clinical characteristics. We believe our study provides several points worth discussing.

With respect to age, a younger age is seen among patients with primary skeletal involvement, as reported in previous single-institution studies [11,12]. However, the mechanisms by which skeletal DLBCL is associated with younger age are currently unclear. In a multivariate model, the survival outcomes in primary bone DLBCL appeared to be similar to nodal cases, indicating that outcomes reported in smaller retrospective studies of primary bone DLBCL should be interpreted in the context of patients' age and proportion of early-stage cases—two previously identified critical prognostic factors [13]. With regard to sex distribution, there was a higher proportion of women among patients with breast and thyroid involvement by DLBCL, which is consistent with previous retrospective studies

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TABLE IV. Multivariate Analysis of Overall Survival in Patients with Diffuse Large B-Cell Lymphoma from the SEER Database (2004–2009), According to Primary Site of Diagnosis

Site of involvement	All patients ($n = 25{,}992$) Multivariate analysis[a] HR (95% CI)	*P*	Stage I/II cases ($n = 11{,}913$) Multivariate analysis[a] HR (95% CI)	*P*
Lymph nodes	Ref.	–	Ref.	–
Gastrointestinal tract	1.24 (1.15–1.33)	<0.001	1.30 (1.18–1.43)	<0.001
Head and neck	0.79 (0.70–0.89)	<0.001	0.82 (0.71–0.95)	0.007
Skin and soft tissue	0.87 (0.76–0.99)	0.04	1.01 (0.86–1.19)	0.87
Genitourinary tract	0.89 (0.77–1.03)	0.11	0.87 (0.72–1.06)	0.18
Skeletal tissue	0.83 (0.69–0.99)	0.04	0.95 (0.74–1.22)	0.69
Respiratory system	1.59 (1.38–1.83)	<0.001	1.81 (1.45–2.25)	<0.001
Hematologic system	0.84 (0.70–1.01)	0.07	-	-
Thyroid gland	0.79 (0.62–1.00)	0.05	0.87 (0.66–1.15)	0.34
Liver/pancreas	1.58 (1.35–1.85)	<0.001	1.89 (1.50–2.38)	<0.001
Breast tissue	0.79 (0.60–1.03)	0.08	0.69 (0.49–0.98)	0.04
Other	1.17 (0.96–1.42)	0.11	1.24 (0.96–1.60)	0.10

P-values <0.004 were considered statistically significant.
[a] Includes age, sex, race, and stage as covariates; coefficients are no listed for clarity.
HR, Hazard ratio; CI, confidence interval.

[14–16]. The rationale behind a female predominance in breast DLBCL is intuitive and mimics the epidemiology of breast cancer. The increased proportion of women in thyroid DLBCL could be explained by a higher proportion of women with Hashimoto's thyroiditis (HT) and the 60-fold increase in the risk of thyroid lymphoma seen in patients with HT [17]; however, half of the patients with thyroid DLBCL will not have a previous history of HT [18], rendering such association as a partial explanation.

On the basis of our study, all extranodal DLBCL sites had a lower proportion of advanced disease at diagnoses when compared with lymph node disease. Similar findings have been reported from Asia [19]. A potential explanation for this finding is that involvement of extranodal sites could be detected earlier based on the symptoms associated with mass effect from the tumor. For example, obstructive symptoms could be more prominent in patients with GI tract, GU tract, liver/pancreas, whereas a palpable mass could become evident early on in patients with H&N, skin/soft tissue, thyroid or breast involvement. Finally, pain could be an early sign in patients with bone involvement.

Racial differences in patients with DLBCL from the SEER database have been previously evaluated [20]. Our study showed worse outcomes in Black patients when compared with White patients. A partial explanation could be that Black patients with DLBCL are less likely to receive rituximab as part of their treatment, based on a recent report by the National Cancer Institute (NCI) Patterns of Care Studies [21], although other studies have not confirmed this finding [22]. The worse outcome seen in Hispanic patients with DLBCL has not been previously reported, and given the paucity of data, additional outcome research is needed in Hispanic population. Race/ethnicity also seems to play a role in the location of extranodal involvement in patients with DLBCL [23]. We found a higher proportion of White patients in skin/soft tissue, respiratory, hematologic, and thyroid DLBCL, a lower proportion of Black patients in skin/soft tissue, breast, and thyroid DLBCL, and a higher proportion of Hispanics in GI tract and liver/pancreas involvement. Such differences could be secondary to biological characteristics of the population. Further studies should focus on the genomic and molecular features of DLBCL according to the race/ethnicity of the patient.

In the survival analysis, we were able to identify extranodal sites with better and worse prognosis. H&N sites appeared as an independent site with a better prognosis when compared with nodal sites. Current data, however, are inconclusive on the prognosis of these patients; few studies have noted a better prognosis [5,24], whereas others have reported a worse prognosis [25]. Other sites of involvement have been associated with a worse prognosis, such as GI tract, respiratory system, liver, and pancreas. Several studies have reported an improved outcome in patients with gastric DLBCL [26,27], although this is likely associated with a better survival in patients with early stages. However, the prognosis in advanced stages has remained poor. There are studies suggesting that the addition of rituximab to chemotherapy might not have positively impacted such patients [28–30]. Data are rather scant in patients with lung DLBCL; a recent study from Mexico suggested a good prognosis in such patients but there was no comparator group [31]. Data on the prognostic value of hepatic or pancreatic involvement is limited, and in a recent Japanese study, these sites were not associated with a worse prognosis [5]; however, the sample size was substantially smaller than ours and could have been underpowered to show a survival difference. Interestingly, our subset analysis on patients with early-stage disease showed a worse outcome in those patients with GI, respiratory, and liver/pancreas sites. These results suggest a different biology of the disease in patients with these extranodal sites.

Our study carries weaknesses inherent to the nature of its design and the limitations of the SEER database. The SEER database provides a population-based real-life setting for epidemiological work but the information available is also limited, allowing for the introduction of bias. Baseline performance status and lactate dehydrogenase levels, known significant prognostic factors in DLBCL [3], could not be studied. Their differential distribution in nodal or extranodal lymphomas might bias our results, although this is plausibly less of an issue in our subanalysis limited to early-stage cases. Previous studies generally showed no difference in the prevalence of poor performance status between nodal and extranodal DLBCL, whereas the results pertaining to elevated lactate dehydrogenase were conflicting [5,16,19,26]. A significant potential source of bias is the lack of central pathological confirmation, which could have introduced classification bias. A second source of bias is the lack of detailed therapy information. SEER provides data on surgery and radiotherapy. However, the main modality of therapy for DLBCL is chemoimmunotherapy. It is possible that the prognostic observations rendered from our analysis would differ if more detailed information on therapy were available. Additional studies using the linked SEER-Medicare database could prove useful on providing additional insight on the outcomes of patients with extranodal DLCBL, and such study is ongoing. A third potential source of bias would be the lack of information on HIV status, as HIV infection has been associated with an increased risk of DLBCL and extranodal

involvement. Finally, stage assignment of extranodal lymphomas, despite strict guidelines set out in the SEER manual, may be problematic even for experienced clinicians, especially with regard to the interpretation of "diffuse" or "multifocal" involvement. For example, about 50% of cases of primary hepatic or pulmonary DLBCL in SEER have a stage assignment different than IV in contradiction to the staging schema. Cases recorded as lymph node primary with Stage IV imply extranodal involvement, but there is no information on the site of involvement. To minimize bias related to these issues, we performed analyses in the aggregate cohort and in the subset of patients with localized (Stage I/II) DLBCL, in which GI, respiratory, and liver/pancreas sites remained significantly associated with a worse prognosis. We should also note that although the SEER data reflect characteristics of the multi-ethnic US population, our results might not be generalizable to extranodal lymphomas in some geographic areas of the world, particularly when considering associations with prevalent HIV, Epstein-Barr virus, and hepatitis B and C infections [32,33].

In conclusion, our study shows that the extranodal site of diagnosis in patients with DLBCL not only are associated with specific clinical characteristics but also seem prognostic for survival in the rituximab era. Future studies should focus on the potential pathological, molecular, and genetic differences between nodal and extranodal DLBCL looking for potential therapeutic targets.

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