

Unstaged Diffuse Large B-Cell Lymphoma in the United States: Predictors and Patient Outcomes

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Abstract. *Background:* Treatment and prognosis of diffuse large B-cell lymphoma (DLBCL) depends on the stage of lymphoma. We conducted this study to examine unstaged DLBCL in the United States. *Materials and Methods:* We used Surveillance Epidemiology and End Result (SEER) 18 registries to select patients with DLBCL diagnosed during January 2000 to December 2012. Limited regional distant Summary stage 2000 was used to determine stage of the disease as localized, regional, distant or unstaged. We used logistic regression to investigate factors associated with unstaged DLBCL. Cox proportional hazards model was used to compare survival outcomes. *Results:* Among 67,765 patients, disease in 3,194 (4.71%) was unstaged. Age (60+ years), non-African American, not married marital status, metropolitan residence, median household income >\$50,000, lymph node as the primary site and those with other primary malignancies before diagnosis of DLBCL were the factors associated with cases being unstaged. The 5-year relative survival rate for patients with unstaged DLBCL was inferior to that of those with localized and regional disease, and superior to that of those with distant disease (hazard ratios of 0.58, 0.66 and 1.24 for localized, regional and distant disease, respectively, when compared to unstaged cases). *Conclusion:* Several factors are associated with higher risk of unstaged DLBCL. Patients with unstaged DLBCL had significantly inferior survival rates compared to patients with localized and regional stage.

Non-Hodgkin lymphoma (NHL) is a group of hematological

malignancies, occurring at an annual incidence of approximately 20 per 100,000 (1). Diffuse large B-cell lymphoma (DLBCL) is the most common type of B-cell NHL, comprising approximately 30% of all cases (2). It is an aggressive cancer that can be cured in over 50% of all patients (3). Staging lymphoma helps define disease location and extent, and also provides a baseline along which treatment response and disease progression can be monitored. In addition, staging helps determine the therapeutic plan for the patient.

However, each year a small percentage of newly diagnosed cancers are not assigned a tumor stage. Merrill *et al.* reviewed the Surveillance, Epidemiology and End Results (SEER) database in order to further characterize the extent of unstaged solid tumor malignancies. They found a higher incidence of unstaged disease in 10 out of 18 cancer types in those of African-American race, in elderly individuals, and in the uninsured (4). Importantly, they reported an inferior 5-year survival in patients with unstaged disease. Similarly, Worthington *et al.* reviewed the SEER database and reported that tumor in 5.1% of patients with colon cancer and 7.8% of those with rectal cancer were unstaged, with characteristics such as older age, African-American race and female sex being associated with a higher likelihood of having unstaged disease (5).

We conducted this study to examine unstaged DLBCL, taking into account both patient characteristics and disease prognosis.

Materials and Methods

Data. SEER is a large population-based database that collects cancer statistics from various sources around the country. The SEER 18 registries were reviewed to select patients diagnosed with DLBCL between January 2000 and December 2012. These 18 registries comprise approximately 27.8% of the US population, and include data from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native Tumor, Greater California, Kentucky, Louisiana, New Jersey, and Greater

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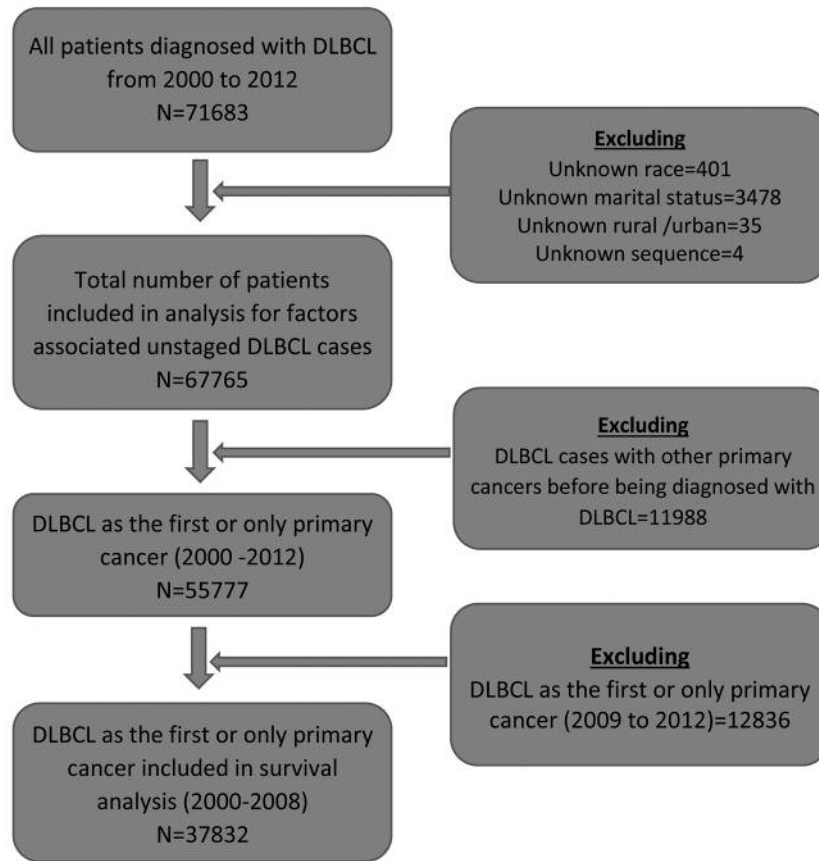


Figure 1. CONSORT diagram for patients with diffuse large B-cell lymphoma (DLBCL).

Georgia (6). These records were sorted, and patients with unknown race, marital status, area of residence or sequence of cancer, were excluded from our study (Figure 1).

Data variables. The patients of the study were divided into various subgroups based on age (0-59 years or 60 years and older), sex (male or female), race (Caucasian, African American, or other), marital status (married, single or separated/divorced/widowed), place of residence (rural, urban or metropolitan), annual household income (\$0-25,000, \$25,000-50,000, or \$50,000 and higher), sequence of cancer (primary DLBCL or other primary malignancy prior to diagnosis of DLBCL) and site of primary malignancy (lymph node, extralymphatic, or unknown site of primary).

Statistical techniques. Local, regional, and distant (LRD) summary staging was used to classify cases of DLBCL. Patient records that did not contain any staging information were categorized as unstaged disease. Factors associated with unstaged cancer were then analyzed using a binomial logistic regression analysis to compute unadjusted (uOR) and adjusted odds ratios (aOR). Corresponding two-sided p-values were calculated, with $p < 0.05$ considered statistically significant.

Relative 3- and 5-year survival (RS) ratios were calculated for the various cohorts based on age, sex, and race, using SEER*Stat software version 8.2.1, National Cancer Institute (Bethesda, MD,

USA) and compared using a z-score and corresponding two-sided p-values. Relative survival is the ratio of the proportion of observed survivors in a cohort of patients with cancer to the proportion of expected survivors in a comparable set of cancer-free individuals within a specific time period. Cox proportion hazards model was used to compare the survival outcomes for different stages of DLBCL, after adjusting for age, sex, and race. Survival curves were then created based on actuarial tables for different cancer stages.

Results

Of the 67,765 patients with DLBCL that were included in the study, 3,194 (4.71%) had unstaged disease. Demographics of patients are included in Table I. Unstaged cases were more common among individuals above the age of 60 years (uOR=1.478, $p < 0.001$; aOR=1.458, $p < 0.001$). After adjusting for variables, males and females were equally likely to be unstaged. Compared to Caucasians, disease in African Americans was less likely to be unstaged (uOR=0.804, $p < 0.005$; aOR=0.835, $p < 0.022$), whereas disease in ‘Other’ races was more likely to be unstaged after adjusting for other variables (uOR=1.109, $p = 0.112$; aOR=1.257, $p = 0.001$).

Table I. Patient demographics.

Parameter	Total, n (%) (N=67765)	Staged, n (%) (N=64571)	Unstaged, n (%) (N=3194)	p-Value*
Age				
<60 Years	22889 (33.8%)	22059 (34.2%)	830 (26.0%)	<0.001
≥60 Years	44876 (66.2%)	42512 (65.8%)	2364 (74.0%)	
Gender				
Male	36855 (54.4%)	35164 (54.5%)	1691 (52.9%)	0.093
Female	30910 (45.6%)	29407 (45.5%)	1503 (47.1%)	
Race				
Caucasian	57703 (85.2%)	54968 (85.1%)	2735 (85.6%)	0.003
African American	4862 (7.2%)	4675 (7.2%)	187 (5.9%)	
Other	5200 (7.7%)	4928 (7.6%)	272 (8.5%)	
Marital status				
Married/living with partner	39051 (57.6%)	37323 (57.8%)	1728 (54.1%)	<0.001
Single	11138 (16.4%)	10633 (16.5%)	505 (15.8%)	
S/D/W	17576 (25.9%)	16615 (25.7%)	961 (30.1%)	
Urbanization				
Rural	999 (1.5%)	946 (1.5%)	53 (1.7%)	0.672
Urban	6847 (10.1%)	6526 (10.1%)	321 (10.1%)	
Metropolitan	59919 (88.4%)	57099 (88.4%)	2820 (88.3%)	
Income [#]				
≤25,000	939 (1.4%)	891 (1.4%)	48 (1.5%)	<0.001
>25,000-50,000	42468 (62.7%)	40278 (62.4%)	2190 (68.6%)	
>50,000	24358 (35.9%)	23402 (36.2%)	956 (29.9%)	
DLBCL sequence				
First or only primary	55777 (82.3%)	53258 (82.5%)	2519 (78.9%)	<0.001
Not first primary	11988 (17.7%)	11313 (17.5%)	675 (21.1%)	
Site of primary				
Lymph nodes	42241 (62.3%)	40090 (62.1%)	2151 (67.3%)	<0.001
Extralymphatic	25322 (37.4%)	24330 (37.7%)	992 (31.1%)	
Unknown	202 (0.3%)	151 (0.2%)	51 (1.6%)	

S/D/W: Separated/divorced/widowed. *Chi-square test. [#]Median annual household income.

Compared to the married population, disease in all other individuals was more likely to be unstaged (uOR=1.026, $p=0.662$; aOR=1.208, $p=0.001$ and uOR=1.249, $p<0.001$; aOR=1.185, $p<0.001$). There were no differences in unstaged cases based on specific areas of residence, but after adjusting for other variables, patients with annual household incomes of >\$50,000 were less likely to have unstaged disease compared to those with household incomes of <\$25,000 (aOR=0.673, $p=0.017$). Similarly, patients with primary cancer discovered prior to the diagnosis of DLBCL, those with extra-lymphatic sites as primary malignancy, and individuals with unknown primary sites, were more likely to be unstaged.

Survival among patients with unstaged DLBCL was greater when compared to those with distant disease (3-year RS of 59.4±1.2% vs. 52.1±0.4%; $p<0.0001$ and 5-year RS of 54.3±1.4% vs. 48.0±0.4%; $p<0.0001$), but was inferior when compared to individuals with localized and regional disease (3-year RS of 59.4±1.2% vs. 73.0±0.4% and 70.9±0.5% with $p<0.0001$ and $p<0.0001$, respectively, 5-

year RS of 54.3±1.4% vs. 69.4±0.5% and 67.7±0.6% with $p<0.0001$ and $p<0.0001$, respectively) (Tables II and III).

Discussion

DLBCL is the most common type of NHL, comprising approximately 30-35% of all cases. Staging cancer is an important prognostic tool, which helps determine the appropriate course of treatment. Each year a proportion of solid tumor malignancies are unstaged (4). Our study revealed that 4.7% of the study population with DLBCL were unstaged. In addition, this cohort of patients had an inferior survival rate compared to those with localized or regional disease. These results are similar to those of Merrill *et al.*, who reported inferior survival in patients with unstaged solid tumor malignancies (4). Gurney *et al.* reviewed the New Zealand Cancer Registry to determine the prevalence and prognosis of different unstaged cancer types (7). They reported that patients with unstaged tumors were significantly less likely to receive definitive surgery. Patients

Table II. Comparison of 3-year relative survival (RS) by stage.

Parameter	Overall 3-year RS + standard error (%)				p-Value: Unstaged vs.		
	Localized	Regional	Distant	Unstaged	Localized	Regional	Distant
All	73.0±0.4	70.9±0.5	52.1±0.4	59.4±1.2	<0.0001	<0.0001	<0.0001
<60 Years	83.0±0.5	82.5±0.6	61.8±0.6	76.0±1.7	<0.0001	<0.0001	<0.0001
≥60 Years	66.4±0.6	62.7±0.8	46.2±0.5	52.2±1.5	<0.0001	<0.0001	0.0011
Male	73.5±0.6	71.0±0.8	52.5±0.5	58.0±1.7	<0.0001	<0.0001	<0.0001
Female	72.4±0.7	78.8±0.6	63.5±0.5	65.7±1.5	<0.0001	<0.0001	0.0328
Caucasian	73.6±0.5	66.9±1.9	53.1±0.4	59.3±1.3	<0.0001	<0.0001	0.0002
AA	67.6±1.7	66.9±1.9	47.5±1.2	57.4±4.5	0.0206	0.0178	0.0592
Other	70.6±1.5	71.7±1.7	47.0±1.3	61.4±3.7	0.0119	0.0020	0.0010

AA: African American.

Table III. Comparison of 5 year relative survival by stages.

Parameter	Overall 5-year RS ± standard error (%)				p-Value: Unstaged vs.		
	Localized	Regional	Distant	Unstaged	Localized	Regional	Distant
All	69.4±0.5	67.7±0.6	48.0±0.4	54.3±1.4	<0.0001	<0.0001	<0.0001
<60 Years	80.2±0.6	80.4±0.7	58.3±0.6	69.5±2.1	<0.0001	<0.0001	<0.0001
≥60 Years	62.0±0.8	58.5±0.9	41.5±0.6	47.7±1.7	<0.0001	<0.0001	0.0003
Male	69.5±0.7	67.6±0.9	47.5±0.6	55.3±1.9	<0.0001	<0.0001	<0.0001
Female	69.3±0.8	67.8±0.9	48.6±0.6	53.2±2.0	<0.0001	<0.0001	0.0354
Caucasian	69.4±0.5	68.0±0.7	49.1±0.5	54.4±1.5	<0.0001	<0.0001	0.0006
AA	65.3±2.0	63.6±2.2	41.8±1.4	51.1±5.2	0.0092	0.0290	0.0856
Other	66.5±1.8	68.1±2.1	41.9±1.5	54.1±4.5	0.0049	0.0008	0.0046

AA: African American.

with unstaged DLBCL may also be less likely to receive aggressive treatment, which may explain the inferior survival outcomes in this population.

We also recorded a higher rate of unstaged disease in the elderly, similar to the results from other studies (4, 5). In a study conducted by Worthington *et al.*, unstaged colon cancer was more likely in older individuals. They postulated that higher rates of unstaged cancer may be seen in the elderly due to a higher number of co-morbid conditions (5). Similarly, Yancik *et al.* reported a higher rate of unstaged breast cancer in elderly patients with co-morbid conditions (8). They suggest that patients with competing co-morbid conditions may be unable to tolerate certain procedures, such as axillary lymph node dissection, due to a compromised health status. In addition, Koroukian *et al.* reported that elderly patients may be less likely to consent to diagnostic work-up (9). Our findings suggest similar trends in elderly patients with DLBCL.

There were no differences in unstaged DLBCL based on gender, contrary to studies that reported a higher proportion of unstaged cancer among females (4). Disease in unmarried

individuals was more likely to be unstaged compared to married patients, which is in concordance with other reports (4, 10, 11). In a study conducted by Goodwin *et al.*, married patients were noted to have superior support systems and socioeconomic stability, resulting in improved staging and treatment outcomes (11). In our study, patients with an annual income of \$50,000 or higher were less likely to have unstaged disease compared to the those with a lower annual income. Bradley *et al.* conducted a study to determine the effects of cancer on nursing home patients and found that Medicaid patients were more likely to have unstaged disease (12). Socioeconomic status may therefore play a significant role in DLBCL staging and treatment, as patients with low annual income may have poor access to insurance and healthcare (12-14).

We found a lower rate of unstaged DLBCL in African Americans compared to Caucasians, in contrast to the Merrill *et al.* study, which reported a higher rate of unstaged cancer of prostate, stomach, colon, rectum, kidney, thyroid, breast, cervix, and ovary in Caucasians (4). In addition, Lathan *et al.* reported higher rates of unstaged non-small cell lung cancer in

African American patients (15), similar to the results from the Merrill *et al*. study. Such racial disparities have been attributed to several factors, including access to care, poor primary care, and perhaps some elemental mistrust of the medical system. More studies are needed to determine why fewer cases of unstaged DLBCL exists in the African American population.

There are several strengths and limitations of our study that warrant consideration. The SEER database provides us with detailed information on patient demographics and disease stage. The data are derived from both urban as well as rural regions, encompassing approximately 27.8% of the US population, adding to the validity of our study. However, disease-specific characteristics, including dose of radiation, number of cycles of treatment received, receipt of chemotherapy or immunotherapy, treatment complications, prognostic features such as lactate dehydrogenase level, performance status, or unfavorable cytogenetics, are not available through the SEER database. In addition, the SEER database does not provide information on co-morbid conditions, which may confound the prognosis of unstaged DLBCL.

Conclusion

In this population-based study, 4.71% of patients with DLBCL had unstaged disease. Older age, single/widowed/divorced marital status, and lower socioeconomic status, were associated with higher rates of unstaged cases. Unstaged DLBCL was associated with inferior survival compared to localized and regional disease.

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