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Research Paper

Socioeconomic and demographic factors contributing to outcomes in patients with primary lymphoma of bone

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ABSTRACT

Background: Primary lymphoma of bone (PLB) is a rare disease, comprising a malignant lymphoid infiltrate of bone. The goal of this study was to identify socioeconomic, demographic, and anatomic factors as prognostic indicators of survival for this disease using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: The SEER database was used to identify a study population of 692 patients diagnosed with PLB in the United States from 1989 to 2003. Survival was analyzed using the Kaplan–Meier method, with effects of potential prognostic factors on survival analyzed using the log-rank test. Multivariable analysis was performed by Cox proportional hazards regression.

Results: The overall 5-year survival rate was 49.6%, with a 10-year survival rate of 30.2%. Median overall survival was 4.9 years (95% CI: 3.9, 6.1). In multivariable analysis, age ($p < 0.0001$), marital status ($p = 0.006$), and appendicular vs. axial tumor location ($p = 0.004$) were found to be independent predictors of survival.

Conclusions: This population-based study of PLB identified age, marital status, and tumor location as independent indicators of prognosis. This finding supports the clinical suspicion that an appendicular tumor location confers a better prognosis than an axial tumor location.

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1. Introduction

The rare disease now known as primary lymphoma of bone (PLB) was initially described by Oberlin [1]. Parker and Jackson later described PLB as a distinct entity [2], which is understood to be a malignant lymphoid infiltrate of bone [3]. While this may include cortical or soft tissue invasion, the diagnosis generally excludes lymph node or distant visceral involvement to be considered a primary lymphoma of bone [4]. This definition has been contended throughout the literature, with some authors permitting lymph node involvement [5–7], though most authors recognize the disease as lymphoma localized only to bone upon diagnosis.

Primary lymphoma of bone affects 1.7/1,000,000 patients in the US [8]. Previous studies have suggested PLB comprise 5% of all extranodal lymphomas [9], and 3% of all bone malignancies [10]. Due to the low incidence of PLB, most prior studies have been from a single-institution, and have had small sample sizes [10–15]. The Surveillance, Epidemiology, and End Results (SEER) database is a publically available database created for the purpose of collecting demographic, clinical, and outcome data for cancer patients in the United States. There remains scant literature published using this database to evaluate larger patient populations [8].

The purpose of this population-based study was to identify prognostic factors for survival in patients with PLB, in order to determine whether disparities in survival exist between demographic cohorts. In doing so, the current study aimed to determine the prognostic significance of different tumor-specific and anatomic considerations that may influence overall survival from this disease. The authors chose to limit this study to adult patients, because PLB in children is often considered and treated as a systemic disease [16].

2. Material and methods

The study population was selected from the National Cancer Institute's SEER database. The SEER database collects data from 18 geographic registries, covering approximately 28% of the U.S.

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population [17]. The SEER*Stat software (Version 8.0.4; NCI; Bethesda, MD) was used to identify 997 adult patients diagnosed with primary lymphoma of bone during a 15-year period from 1989 to 2003. Histology was selected by using ICD-O-3 codes 9590/3, 9591/3, 9670/3, 19671/3, 9675/3, 9680/3, and 9684/3. Primary site was selected as C40.0, C40.1, C40.2, C40.3, C40.8, C40.9, C41.2, C41.3, C41.4, and C41.9. Exclusion criteria included lesions of the skull and face, T-cell lymphoma, and cases without follow up data, yielding a final study population of 692 patients.

Tumor location was dichotomized as either appendicular or axial. The scapula was considered to be part of the appendicular skeleton, while the pelvic bones were considered to be part of the axial skeleton. Marital status was categorized as single, married, or other (including separated, divorced or widowed). Rural–urban continuum code was collapsed into a binary variable: Metro county or non-metro county, using guidelines by SEER and the Economic Research Service [18,19]. SEER registry region was aggregated into regions (Northeast, South, Southwest, Midwest, and West). Race was categorized as White, Black or Asian/Other. Age was considered as a categorical variable (<30 years, 30–59 years, ≥ 60 years).

Statistical analysis was performed in SAS version 9.3 (SAS Institute, Cary, NC). The effects of categorical variables on survival were assessed by computing Kaplan–Meier product limit curves and compared using the log-rank test. The effects of continuous variables were analyzed using Cox proportional hazards regression. The Bonferroni method was applied when performing multiple comparisons. Factors that appeared to be significantly associated with survival in the univariate analysis were considered for inclusion in the final multivariable Cox proportional hazards regression model. A result was considered statistically significant with a p-value <0.05. Efron's method was used to adjust for tied failure times.

Incidence rates were age-adjusted to the 2000 US standard population, with confidence intervals calculated using the Tiwari modification. Annual percentage change was calculated using the weighted least squares method.

3. Results

The final analysis included 692 patients, whose demographic and clinical characteristics are presented in Table 1. The majority of patients were white (89.0%), non-Hispanic (91.3%), and lived in metropolitan counties (87.4%). The majority of patients were over the age of 60 years (55.6%), and diffuse large B-cell lymphoma was the most common histologic classification (71.2%). The western region of the United States contributed the largest proportion of patients to the study population (56.5%).

The estimated overall survival of patients for all patients in this study was 49.6% at 5-years, and 30.2% at 10-years (Fig. 1). The incidence of PLB during the 15-year study period ranged from 0.1/100,000 to 0.3/100,000 (Fig. 2). The annual percent change for this time period was non-significant, suggesting a stable incidence over the study period.

In univariate analysis, significant factors for overall survival included age ($p<0.0001$), marital status ($p<0.0001$), anatomic location of tumor ($p<0.0001$), geographic region ($p=0.02$), and tumor grade ($p=0.01$). After Bonferroni adjustment, tumor grade was no longer a significant prognostic indicator for overall survival. Furthermore, after Bonferroni adjustment for multiple comparisons, tumor grade and geographic region were not statistically significantly associated with overall survival. Univariate analysis results for categorical variables are presented in Table 2. Kaplan–Meier product limit curves are provided for age (Fig. 3), marital status (Fig. 4), and tumor location (Fig. 5).

Table 1
Descriptive demographic and clinical statistics of the study population.

Characteristic	Frequency	% Of total
Total number of patients	692	100.0
Age		
<30	67	9.7
30 to 59	240	34.7
60 or greater	385	55.6
Sex		
Male	370	53.5
Female	322	46.5
Race		
White	616	89.0
Black	45	6.5
Asian, other and unknown	31	4.5
Ethnicity		
Non-Spanish–Hispanic–Latino	632	91.3
Spanish–Hispanic–Latino	60	8.7
Marital status		
Single	122	18.2
Married	383	57.2
Divorced, separated, widowed	165	24.6
Geographic region		
Southeast	54	7.8
South	42	6.1
Midwest	111	16.0
Northeast	94	13.6
West	391	56.5
County		
Non-metro county	87	12.6
Metro county	605	87.4
Tumor site		
Axial	389	56.2
Appendicular	303	43.8
Histology		
Malignant lymphoma, NOS[a]	46	6.7
Malignant lymphoma, non-Hodgkin, NOS[a]	75	10.8
Malignant lymphoma, small B lymphocytes, NOS[a]	21	3.0
Lymphoplasmacytic lymphoma (NHL [b])	11	1.6
Malignant lymphoma, mixed small and large cell, diffuse	22	3.2
Diffuse large B-cell (NHL[b]) lymphoma	493	71.2
Malignant lymphoma, large B, diffuse, immunoblastic	24	3.5
Grade		
B-cell; pre-B; B-precursor	668	96.5
Well differentiated; grade I	6	0.9
Moderately differentiated; grade II	9	1.3
Poorly differentiated; grade III	5	0.7
Undifferentiated; anaplastic; grade IV	4	0.6
Surgery		
Yes	177	25.8
No	510	74.2
Radiation		
Yes	475	70.6
No	198	29.4

[a] NOS, not otherwise specified.
[b] NHL, non-Hodgkin lymphoma.

The final multivariable model demonstrated that age ($p<0.0001$), marital status ($p=0.02$), and appendicular or axial tumor location ($p=0.004$) remained significant independent prognostic variables for overall survival (Table 3). A survival advantage was demonstrated for younger patients. The mortality rate for PLB patients in the 30–59 age group is estimated to be 4.4 times that for those patients in the <30 age group, after adjusting for marital status and tumor location (CI: 1.7–11.2; $p=0.002$). Furthermore, patients aged 60 or older are estimated to have a mortality rate 12.8 times that for <30 year-old

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