Original Article

Characterization and outcomes of local treatment for primary bladder lymphoma: A population-based cohort analysis

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Abstract

Introduction: Primary bladder lymphoma (PBL) is rare, representing 0.2% of extranodal lymphoma and less than 1% of all tumors originating in the bladder. Since the initial description of the disease, low-grade mucosa-associated lymphoid tissue (MALT) lymphoma has been reported as the most common subtype while high-grade disease was thought to represent only 20% of the reported cases.

Materials and Methods: One hundred and ninety five patients with PBL from the Surveillance, Epidemiology, and End Results (SEER) registry from 1998-2010 were reviewed. Tumors were classified as high or low grade based on histologic subtype of lymphoma based on revised European-American Lymphoma classification system. Socio-demographic and clinical variables were reported, as well as survival outcome analyses using the Kaplan-Meier method and log-rank test. Cox proportional hazard analysis was used to generate hazard ratios for risk factors associated with mortality.

Results: Eighty-three patients (42.6%) with low-grade and 112 patients (57.4%) with high-grade bladder lymphoma were studied. There were no differences between the low and high-grade groups for socio-demographic or clinical variables. Median overall survival or patients with low-grade disease was 38 months versus 15 months for patients with high-grade disease ($p<0.001$). Analysis demonstrated worse survival outcomes for patients with high-grade disease compared to low-grade disease ($p<0.001$). On multivariable analysis, increasing age and high-grade disease were associated with worse disease specific mortality ($p<0.001$).

Conclusion: Patient with high-grade primary bladder lymphoma had worse survival outcomes compared to those with low-grade disease. While transurethral resection provides tissue for diagnosis, immunotherapy/chemotherapy remains the mainstay of treatment for bladder lymphoma. Consolidation chemotherapy has been recommended in young patients not achieving complete remission with immunotherapy/chemotherapy.

Keywords: Bladder cancer; lymphoma; outcomes; SEER

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INTRODUCTION

Malignant lymphoma of the bladder was first described in 1885 by Eve and Chaffney and can be classified as either primary lymphoma or secondary (metastatic) lymphoma.[1,2] Primary lymphoma of the bladder is rare, representing only 0.2% of extranodal lymphoma (25%–40% of all lymphoma) and <1% of all primary bladder tumors.[2-4] Like other malignancies of the bladder, the most common presenting symptom is gross hematuria. Unlike bladder urothelial carcinoma, bladder lymphoma is seen in women two to three times more often than in men.[2,5] The mean age at diagnosis ranges from 40 to 80 years of age and the underlying cystitis is reported in 22%–33% of cases. Therefore, cystitis has been theorized as a possible etiology of primary lymphoma in an organ that lacks hematopoietic and lymphoid tissue.[2,5,6] However, given the extremely common occurrence of cystitis and rarity of bladder lymphoma, the role of cystitis is at best a component of a multifactorial process. On the whole, bladder lymphoma has a favorable prognosis when compared to other types of bladder cancer.[2,5]

The most common subtype of bladder lymphoma is low-grade extranodal marginal zone/mucosa-associated lymphoid tissue (MALT) lymphoma, comprising approximately 86% of all low-grade cases and 53% of the total reported cases.[2,3,5] High-grade tumors are thought to represent as few as 20% of the reported cases, with the most common type being diffuse large B-cell lymphoma (DLBCL).[2]

There remains a paucity of literature for primary bladder lymphoma (PBL), and treatment and survival outcomes have largely been based on small case series. Therefore, the objective of this study was to further clarify the epidemiology, demographics, local treatment, and outcomes of patients with PBL using a population-based cohort. In an effort to help guide future clinical treatment, the patients analyzed in this study were separated into low- and high-grade disease groups.

MATERIALS AND METHODS

Study population

The study cohort consisted of patients from all 18 registries comprising the Surveillance, Epidemiology, and End Results (SEER) database, which reports cancer-specific outcomes from specific geographic areas representing 28% of the US population.[7] Patients ≥18 years of age with primary lymphoma of the bladder between 1998 and 2010 were identified utilizing the primary site codes C67.0-C67.9, and International Classification of Diseases for Oncology, 9th edition codes 9670/3 (small B-cell lymphoma), 9671/3 (lymphoplasmacytic lymphoma), 9673/3 (mantle cell lymphoma), 9680/3 (DLBCL), 9684/3 (immunoblastic DLBCL), 9687/3 (Burkitt's lymphoma), 9690/3 (follicular lymphoma), 9695/3 (follicular lymphoma), 9698/3 (follicular lymphoma), 9699/3 ([MALT] lymphoma), and 9714/3 (anaplastic large T-cell lymphoma) for a study cohort of 195 patients. Patients were classified as low grade or high grade based on the specific subtypes of lymphoma from the revised European-American lymphoma classification system.[8-10] The low-grade group included malignant lymphoma, small B-lymphocytes, n = 16; lymphoplasmacytic lymphoma, n = 2; mantle cell lymphoma, n = 2; follicular lymphoma, n = 10; and MALT lymphoma, n = 53. The high-grade cohort included DLBCL, n = 101; DLBCL, immunoblastic, n = 4; Burkitt's lymphoma, n = 3; and anaplastic large T-cell lymphoma, n = 4.

Description of variables

Sociodemographic variables of interest included age at diagnosis, gender, race (black vs. white vs. other), marital status (married vs. single/divorced/widowed), and median census county data for educational attainment (percentage <9th grade education), percentage of unemployed, and household income. Clinical variables included surgical treatment (none vs. transurethral resection of bladder tumor [TURBT] vs. radical cystectomy), radiation treatment (none vs. beam radiation only vs. adjuvant beam radiation), SEER stage (localized vs. regional vs. distant), and cause of death (alive vs. dead of disease vs. dead of other causes). Median overall survival (OS) and disease-specific survival (DSS) were calculated (censoring date September 10, 2013). The regimen of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone) has proven to be successful in treating PBLs, either as solitary treatment or in combination therapy.[1,4,5,11] However, the SEER database lacks documentation of chemotherapy-specific data and thus prevented a more in-depth analysis of outcome analysis of R-CHOP chemotherapy.

Statistical analyses

Descriptive statistics for sociodemographic and clinical variables were performed using Chi-square test. Survival estimates were calculated using the Kaplan–Meier method for OS and DSS by disease grade. Cox proportional hazard analysis was performed to generate hazard ratios (HRs) for risk factors of disease-specific mortality. The model was

constructed and analyses were performed using backward selection, removing all insignificant variables until the best-fit model was achieved. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). All tests were two sided and with a statistical significance set at $P < 0.05$.

RESULTS

Population, sociodemographics, and clinical outcomes

There were 83 patients (42.6%) with low-grade and 112 patients (57.4%) with high-grade bladder lymphoma [Table 1]. The median age for low-grade disease was 74 years (interquartile range [IQR]: 15) and 77 years (IQR: 17) for high-grade disease ($P = 0.06$). There were no differences between the low- and high-grade disease groups for gender ($P = 0.62$), race ($P = 0.16$), and marital status ($P = 0.77$). Patients with low-grade bladder lymphoma had a county median household income of $6,144 (IQR: $1,515) versus $5,655 (IQR: $1,878) for patients with high-grade disease ($P = 0.06$). There were no differences between the grade stratification groups for surgical treatment ($P = 0.72$) or radiation treatment ($P = 0.58$) [Table 2]. Patients with low-grade disease were more likely to have localized disease (71.0%) compared to those with high-grade disease (51.8%). Similarly, low-grade disease was less likely to progress to distant disease (18.1%) than high-grade bladder lymphoma (25.9%) ($P = 0.01$).

Factors associated with survival

Median OS for patients with low-grade disease was significantly higher at 38 months (IQR: 48 months) in contrast to median OS of 15 months (IQR: 53 months) for patients with high-grade disease ($P < 0.001$). Kaplan–Meier analysis for both DSS [Figure 1] and OS [Figure 2] demonstrated worse survival outcomes for patients with high-grade disease compared to low-grade disease (both $P < 0.001$). On Cox proportional hazard analysis, disease grade remained the most significant risk factor for disease-specific mortality (HR: 5.41, 95% confidence interval [CI]: 2.55–11.47, $P < 0.001$) [Table 3]. Furthermore, increasing age was also predictive of mortality (HR: 1.04, 95% CI: 1.02–1.07, $P < 0.001$).

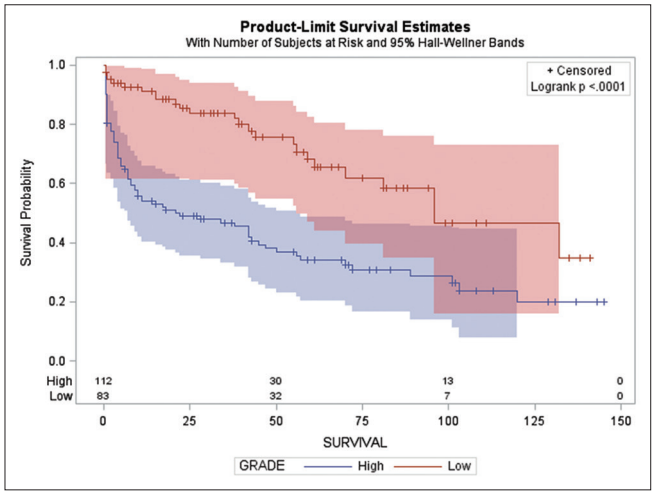

Figure 1: Kaplan-Meier analysis for disease specific survival (p<0.0001)

DISCUSSION

Table 1: Sociodemographic variables of patients with primary bladder lymphoma

Variable	Low grade (*n*=83)	High grade (*n*=112)	*P*
Median age, years (IQR)	74 (15)	77 (17)	0.06
Gender, *n* (%)			
Male	34 (41)	42 (38)	0.62
Female	49 (59)	70 (62)	
Race, *n* (%)			
White	77 (93)	94 (84)	0.16
Black	3 (4)	5 (4)	
Other	2 (2)	12 (11)	
Unknown	1 (1)	1 (1)	
Marital status, *n* (%)			
SDW	29 (35)	43 (38)	0.77
Married	50 (60)	62 (56)	
Unknown	4 (5)	7 (6)	
Median %percentage <9th grade education (IQR)	7.3 (5.9)	5.3 (5.2)	0.13
Median %percentage of unemployed (IQR)	8.9 (2.0)	9.2 (2.5)	0.31
Median household income, $ (IQR)	6.144 (1.515)	5,655 (1.878)	0.06

IQR: Interquartile range, SDW: Single/divorced/widowed

Table 2: Clinical variables and survival outcomes of patients with primary bladder lymphoma

Variable	Low grade (*n*=83)	High grade (*n*=112)	*P*
SEER staging, *n* (%)			
Localized	59 (71)	58 (51)	0.01
Regional	6 (7)	23 (21)	
Distant	15 (18)	29 (26)	
Unstaged	3 (4)	2 (2)	
Surgery, *n* (%)			
None	32 (39)	41 (37)	0.72
TURBT	49 (59)	65 (58)	
Radical cystectomy	2 (2)	5 (4)	
Unknown	0	1 (1)	
Radiation, *n* (%)			
None	62 (75)	84 (75)	0.58
Adjuvant beam radiation	17 (20)	19 (17)	
Beam radiation only	4 (5)	7 (6)	
Unknown	0	2 (2)	
Status, *n* (%)			
Alive	58 (70)	38 (34)	<0.001
Dead	25 (30)	74 (66)	
Survival statistics, *n* (%)			
Alive	58 (70)	38 (34)	<0.001
Dead of disease	11 (13)	45 (40)	
Dead of other cause	14 (17)	29 (26)	
Median survival, months (IQR)	38 (48)	15 (53)	<0.001

TURBT: Transurethral resection of bladder tumor, SEER: Surveillance, Epidemiology, and End Result, IQR: Interquartile range

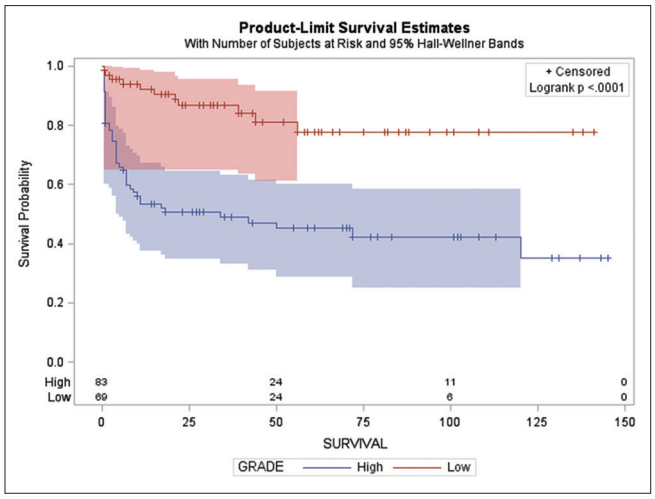

Figure 2: Kaplan-Meier analysis for overall survival (p<0.0001)

Table 3: Risk factors associated with disease-specific mortality in patients with primary bladder lymphoma

Variable	HR	95%CI	*P*
Stage			
Regional versus localized	1.10	0.50–2.43	0.81
Distant versus localized	1.57	0.82–2.99	0.17
Unstaged versus localized	9.96	2.70–36.76	<0.001
Age	1.04	1.02–1.07	<0.001
Grade			
High versus low	5.41	2.55–11.47	<0.001
Surgery			
Local versus none	0.78	0.42–1.45	0.43
Radical cystectomy versus none	0.61	0.17–2.28	0.47
Unknown versus none	0.39	0.02–6.94	0.52
Radiation			
Beam only versus none	0.84	0.28–2.55	0.76
Adjuvant beam versus none	0.63	0.26–1.52	0.30
Unknown versus none	2.71	0.33–22.21	0.35

CI: Confidence interval, HR: Hazard ratio

In this population-based analysis of PBL, we found that the disease was more common in women and Caucasians. The overall incidence was 1.5 times greater in women than in men and the disease presented in Caucasians in 87.7% of all cases, similar for both low- and high-grade lymphomas. Furthermore, there were no differences in sociodemographic and clinical variables between the two groups. Patients with high-grade disease had worse outcomes compared to those with low-grade disease who had poorer overall DSS.

Kempton *et al*. were the first to report on low-grade disease in the 1990s after conducting a retrospective study using the Mayo Clinic tissue registry from 1940 to 1996.[3] Among 36 total cases of bladder lymphoma, six of which were primary, all were low-grade MALT lymphoma.[3] Hughes *et al*., who analyzed the Scotland and Newcastle Lymphoma Group database from 1980 to 2001, also found low-grade MALT lymphoma (50% or 6/12 cases) to be the most common PBL followed by high-grade DLBCL (33% or 4/12 cases).[5] Further studies have suggested that DLBCL is the most common subtype of high-grade PBL.[5,8] In the current analysis of SEER from 1998 to 2010, the most common overall subtype of PBL was high-grade DLBCL (51.7%). Low-grade MALT lymphoma was the most common low-grade subtype of PBL. MALT was the second most common subtype comprising 28.2% of all PBLs. The apparent increasing proportion of DLBCL is observed despite reported stable incidence in the Netherland Cancer Registry.

Most studies have reported that women present with bladder lymphoma more often than men,[3,5,12] which coincides with our finding that women are 1.5 times more likely to be affected. Although none of the previous studies reported patients' race, it is worth noting the predominance of Caucasians recorded in the SEER database with bladder lymphoma.

When comparing the survival rates between low- and high-grade diseases, we found patients with high-grade disease to have significantly worse survival. Low-grade bladder lesions are described as taking a more indolent, less invasive course with a favorable prognosis.[2,8] Freedman *et al*. reported that high-grade bladder lymphomas are more aggressive and without treatment have a poor prognosis of only a few months. We found that low-grade lesions had an OS of 69.9% with a median of 38 months (disease-specific death rate: 13.3%), while high-grade lesions only had an OS of 33.9% with a median of 15 months (disease-specific death rate: 40.2%). Furthermore, high-grade disease and increasing age were the only factors predictive of disease-specific mortality when analyzed in a multivariable model.

Appropriate treatment of PBL requires the stage of the lesion to be known to maximize outcomes and minimize treatment toxicity. Patients with low-grade tumors respond well to local therapy, and as such TURBT should be performed initially, particularly for tissue diagnosis.[5,13,14] Radiation as either a primary or adjuvant treatment has also been successful in treating this disease, however it subjects patients to increased side effects compared to a TURBT alone.[5,15] For all high-grade lesions and any recurrent low-grade tumors, chemotherapy is the treatment of choice. The regimen of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone) has proven to be successful in treating PBLs, either as solitary treatment or in combination therapy.[1,4,5,11] Johnson *et al*. found that high-grade tumors such as DLBCL, which are positive for the BCL-2 gene translocation, may

have a better prognosis if rituximab is added to CHOP therapy to help overcome the chemotherapy resistance by inducing cell apoptosis through the BCL-2-regulated mitochondrial pathway.[16-18] Chemotherapy also provides the benefit of treating early systematic disease which has not yet been detected in high-grade lesions.[15] The role of radical or partial cystectomy is poorly understood and has only been sporadically reported. Of the cases reporting radical cystectomy, most are accompanied by adjuvant chemotherapy or radiation.[5] Based on the efficacy of chemotherapy, we recommend that cystectomy should be reserved for unique circumstances in which R-CHOP therapy cannot be utilized for high-grade lesions.

The strength of this study is that it represents the largest cohort of PBL to report clinical, sociodemographic, and long-term survival outcomes. However, the study does not lack limitations. The SEER database lacks documentation of chemotherapy-specific data and thus prevented a more in-depth analysis of outcome analysis of R-CHOP chemotherapy. Furthermore, the SEER database does not report comorbidities and may account for treatment-specific decisions. This also limited our ability to report the most common presenting symptoms, as well as address the number of patients with preexisting or underlying cystitis.

CONCLUSIONS

In this population-based cohort of patients with PBL, patients with high-grade disease had worse survival outcomes compared to those with low-grade disease. On multivariable analysis, only increasing age and disease grade were predictive of disease-specific mortality. Furthermore, there were minimal sociodemographic and treatment modality differences between low- and high-grade disease patients. PBL remains a rare disease with a poor prognosis in patients with high-grade disease. Further studies are needed to delineate appropriate treatment algorithms to optimize disease control and systemic toxicity.

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Conflicts of interest
There are no conflicts of interest.

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