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Original Research Article

An Observational Study to Assess the Primary Lymphomas of the Genitourinary Tract

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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to assess the primary lymphomas of the genitourinary tract.

Material & Methods: The present study was conducted in the Department of Surgery, for the period of 12 months and 200 patients were included in the study.

Results: Median age at presentation was 71 years, with only 25% of cases occurring in patients younger than 60 years old. The predominant site of involvement was the kidney (70%). The most frequently encountered stage at presentation was stage I (40% of cases), followed by stage IV (32% of cases). The majority of cases did not receive radiation therapy or undergo cancer-directed surgery while 35% of the patients only underwent cancer-directed surgery, 5% received only radiation therapy, and 6% had multimodal treatment (radiation therapy combined with cancer-directed surgery). In terms of histology, the three most prevalent types of PUTL were DLBCL followed by marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma and follicular lymphoma. Variables that were included were age, race, treatment, site, stage, year, gender and type of lymphoma. Older age groups had worse CCS. Male gender also conferred a worse prognosis. Compared with stage III-IV, patients with stage I disease had better CSS. Stage II did not reach statistical significance. Cancer-directed surgery and multimodal treatment (surgery plus radiation therapy) were associated with a mortality benefit, while the administration of radiation therapy alone did not improve outcomes. DLBCL carried the worst prognosis, with follicular and MALT lymphomas demonstrating better outcomes.

Conclusion: We found that primary urinary tract DLBCL carries a worse prognosis than nodal DBLCL in both early and late stages. In addition, surgery may be beneficial for patients with PUTL. The survival of patients with PUTL in the past two decades has not improved significantly despite the introduction of modern therapies such as rituximab. Therefore, better therapies are needed.

Keywords: Primary Extranodal Lymphoma; Prostate Lymphoma; Renal Lymphoma; Testis Lymphoma; Survival.

Introduction

The incidence of lymphoma ranks among the top five malignant neoplasms. [1] Lymphomas can arise in almost every organ or site, and approximately one-third of the patients have extranodal origin. [2] Among them, less than 5% were genito-urinary lymphomas. [3] Extranodal lymphomas, however, comprise a minority of cases: approximately 25–40%, depending on the criteria used. [4] Lymphomas arising in the urinary tract and male genital organs including the kidney, bladder, prostate, testis, ureter/urethra, and penis account for less than 5% of extranodal lymphomas. Renal involvement in lymphoma commonly occurs in the presence of widespread nodal or extranodal lymphoma and is classified as secondary renal lymphoma (SRL). However, lymphoma may rarely involve the kidneys alone without evidence of disease elsewhere; then, it is termed "primary renal lymphoma" (PRL). [5,6]

Primary urinary tract lymphoma (PUTL), first described in 1953, [7] is a very rare entity, with only a few case reports in the literature. [8,9] Genitourinary tract NHLs represent 8.4% of extranodal lymphomas. [10] The origin of primary extranodal lymphoma within the genitourinary (GU, PGUL) tract is extremely rare. Of all PGUL, testicular primary lymphoma (testis-PL) is the most common type. [11] Conversely, those originate from the kidney (renal-PL), the bladder (bladder-PL) and the prostate (prostate-PL) cumulatively account for less than 0.5% of all tumors affecting these three organs. [12]

Although the diagnosis of renal lymphoma can be challenging, an awareness of the spectrum of imaging findings can help to differentiate lymphoma from other renal malignancies such as renal cell carcinoma (RCC) and can lead to appropriate recommendations for biopsy. On ultrasound, renal lymphoma is usually hypoechoic or anechoic. [11] Diffuse nephromegaly may also be seen. However, ultrasound is less sensitive than contrast-enhanced CT for detecting renal lymphoma. Further, sonographic appearances of renal lymphoma are usually nonspecific and lead to further investigation with CT or MRI.

Hence the aim of the present study was to assess the primary lymphomas of the genitourinary tract.

Materials & Methods

The present study was conducted in the Department of Surgery, Netaji Subhas Medical College and hospital, Bihta, Patna, Bihar, India India for the period of 12 months and 200 patients were included in the study.

We also relied on the International Classification of Diseases ninth edition codes to identify NHL[13], tumor of the testis (GCTT, both seminomatous [SGCT] and non seminomatous [NSGCT]), renal cell carcinoma (RCC), transitional cell carcinoma of the bladder (TCC) and adenocarcinoma of the prostate (PCa) cases.[14] Lymphomas were classified as either low or high grade, based on World Health Organization classification system.[15] All autopsy or death certificate cases were excluded. In order to identify only PGUL and therefore exclude secondary extranodal involvement, we included only patients with localized disease (SEER stage code). Consequently, all patients with either clinical or pathological lymph-node involvement, as well as those with metastatic disease, were excluded. Covariates included age at diagnosis, gender, race, marital status, year of diagnosis, residence area, socioeconomic status and surgical treatment.

Statistical Analysis: Statistical analyses consisted of four analytical steps and applied to all four groups. First, rates of PGUL were estimated. Second, we examined the estimated annual percentage changes (EAPCs) of surgically-treated testis-PL, renal-PL, bladder-PL and prostate-PL. The EAPC is calculated using a generalized linear model under the assumption of linearity on the log scale, which is equivalent to a constant change assumption.[16] Third, multivariable logistic regression models predicting the risk of diagnosis of PGUL were fitted. Co-variates consisted of age, gender, marital status, race and year of diagnosis. Fourth, cumulative incidence plots depicted the cancer-specific mortality (CSM) and other-cause mortality (OCM) rates in testis-PL vs. GCT, renal-PL vs. RCC, bladder-PL vs. TCC and prostate- PL vs. PCa. Finally, multivariable competing risks regression (CRR) models tested for CSM after adjustment for OCM in all the four groups. Adjustment variables consisted of histo- logical type, age, gender, race and year of diagnosis. All statistical tests were two-sided with a level of significance set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics

Results

Table 1: Clinical and demographic characteristics of patients with primary urinary tract lymphoma

Characteristics	N	%
Age groups		
<60 Years	50	25
60-75 Years	80	40
>75 Years	70	35
Gender		
Male	120	60
Female	80	40
Marital status		
Married	110	55
Single	28	14
Widowed	40	20
Divorced	14	7
Unknown	8	4
Site		
Kidney	140	70
Pelvis	4	2
Ureter	3	1.5
Bladder	53	26.5
Ann-Arbor stage		
I	80	40
II	44	22

III	12	6
IV	64	32
Cancer-directed surgery		
Yes	116	58
No	84	42
Radiation		
Yes	24	12
No	176	88
Treatment		
Surgery only	70	35
Radiation only	10	5
Both	12	6
Unknown	4	2
Neither	104	52
Type of lymphoma		
DLBCL	104	52
MALT	24	12
Follicular	20	10
NHL, NOS	20	10
Malignant lymphoma, NOS	10	5
CLL	8	4
Burkitt	6	3
Other NHL, B-cell	4	2
Hodgkin	2	1
Other lymphomas	1	0.5
Other NHL, T-cell	1	0.5

Median age at presentation was 71 years, with only 25% of cases occurring in patients younger than 60 years old. The predominant site of involvement was the kidney (70%). The most frequently encountered stage at presentation was stage I (40% of cases), followed by stage IV (32% of cases). The majority of cases did not receive radiation therapy or undergo cancer-directed surgery while 35% of the patients only underwent cancer-directed surgery, 5% received only radiation therapy, and 6% had multimodal treatment (radiation therapy combined with cancer-directed surgery). In terms of histology, the three most prevalent types of PUTL were DLBCL followed by marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma and follicular lymphoma.

Table 2: Cox proportional hazards model for cancer-specific survival in patients with primary urinary tract lymphoma.

	Variable	**Hazard ratio**	***p*-Value**	**95% CI**	***p*-Value**
Histology	DLBCL	Referent		0.31-0.74	0.001
	Follicular	0.48		0.08-0.33	<0.001
	MALT	0.16			
Gender	Female	Referent			
	Male	1.48		1.13-1.94 0.004	1.48
Stage	I	0.55		0.40-0.76	<0.001
	II	0.73		0.53-1.01	0.06
Site	Kidney	0.77		0.55-1.07 0.117	0.77
	Bladder	Referent			-
Treatment	No radiation or surgery	Referent			-
	Only surgery	0.70		0.53-0.93 0.015	0.70
	Only radiation	0.84		0.49-1.43 0.515	0.84
	Surgery and radiation	0.41		0.22-0.77 0.005	0.41
Age groups	<60	Referent			
	60-75	1.97		1.40-2.78	<0.001
	>75	2.72		1.91-3.90	<0.001

Variables that were included were age, race, treatment, site, stage, year, gender and type of lymphoma. Older age groups had worse CCS. Male gender also conferred a worse prognosis. Compared with stage III-IV, patients with stage I disease had better CSS. Stage II did not reach statistical significance. Cancer-directed surgery and multimodal treatment (surgery plus radiation

therapy) were associated with a mortality benefit, while the administration of radiation therapy alone did not improve outcomes. DLBCL carried the worst prognosis, with follicular and MALT lymphomas demonstrating better outcomes.

Discussion

Approximately one-third of NHL arise from sites other than lymph nodes, spleen or the bone marrow. Primary extranodal lymphomas are defined as lymphomas with no or only minor nodal involvement associated with a clinically dominant extranodal component. They can virtually originate in almost every organ. [17] The origin of primary extranodal lymphoma within the genitourinary (GU, PGUL) tract is extremely rare. Of all PGUL, testicular primary lymphoma (testis-PL) is the most common type. [18] Conversely, those originate from the kidney (renal-PL), the bladder (bladder-PL) and the prostate (prostate-PL) cumulatively account for less than 0.5% of all tumors affecting these three organs. [19]

Median age at presentation was 71 years, with only 25% of cases occurring in patients younger than 60 years old. The predominant site of involvement was the kidney (70%). The most frequently encountered stage at presentation was stage I (40% of cases), followed by stage IV (32% of cases). The majority of cases did not receive radiation therapy or undergo cancer-directed surgery while 35% of the patients only underwent cancer-directed surgery, 5% received only radiation therapy, and 6% had multimodal treatment (radiation therapy combined with cancer-directed surgery). In terms of histology, the three most prevalent types of PUTL were DLBCL followed by marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma and follicular lymphoma. In addition, the observation that bladder lymphomas occur more frequently in women than men could support the above theory since women experience cystitis more frequently than men. Moreover, higher frequency of MALT-associated lymphoma, which is commonly associated with bacterial infections [20], was noted in the bladder. A previous study failed to demonstrate an association between kidney lymphoma and Epstein-Barr virus infection. [21]

Castillo et al. demonstrated that gastrointestinal, pulmonary and liver/pancreas DLBCL carry a worse prognosis than nodal.[10] In our analysis, after controlling for gender, patient age and race, disease stage and year of diagnosis, we showed for the first time that PUTL of DLBCL type is associated with worse CSS compared with primary nodal DLBCL in both early (I-II) and late (III-IV) stages. This could potentially be explained by the comorbidities that are caused by mass effect in the urinary tract (hydronephrosis) and infiltration of the renal parenchyma which leads to acute kidney injury. Any type of kidney injury in patients with cancer is associated with worse outcomes. [22] When comparing kidney with bladder lymphoma, a few differences were noted. Patients with bladder lymphoma were mainly female whereas those with kidney lymphoma were mainly male. Moreover, a higher frequency of MALT-associated lymphoma was noted in the bladder, which according to the literature is most commonly associated with bacterial infections. [20] Variables that were included were age, race, treatment, site, stage, year, gender and type of lymphoma. Older age groups had worse CCS. Male gender also conferred a worse prognosis. Compared with stage III-IV, patients with stage I disease had better CSS. Stage II did not reach statistical significance. Cancer-directed surgery and multimodal treatment (surgery plus radiation therapy) were associated with a mortality benefit, while the administration of radiation therapy alone did not improve outcomes. DLBCL carried the worst prognosis, with follicular and MALT lymphomas demonstrating better outcomes. Among the three most prevalent PUTL histology subtypes in our analysis, DLBCL carried the worse prognosis, whereas patients diagnosed with MALT-associated lymphoma had the best prognosis. Female gender was also independently associated with better survival. Similar data have been reported for B-cell lymphomas in the era of rituximab but were not noticed before supporting the fact that women may respond better to rituximab. [23,24]

Conclusion

We found that primary urinary tract DLBCL carries a worse prognosis than nodal DBLCL in both early and late stages. In addition, surgery may be beneficial for patients with PUTL. The survival of patients with PUTL in the past two decades has not improved significantly despite the introduction of modern therapies such as rituximab. Therefore, better therapies are needed.

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